Beyond Steroids: Therapy of Immune-Mediated Skin Disease
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Definitions
- **Autoimmune disease** - etiopathogenesis involves the production of host antibodies and/or immunocompetent lymphocytes directed against "self" (host) antigens resulting in primary damage to the host's tissues. Autoimmunity should be demonstrable by in vitro and in vivo techniques.
- **Immune-mediated disease** - broader term; etiopathogenesis involves tissue damage caused by the body's immune system. Synonyms include "allergy" and "hypersensitivity". Classically, four basic mechanisms of immune injury may be involved: type I (anaphylactic), type II (cytotoxic), type III (immune complex) and IV (cell-mediated).

The role of antibiotics
- Secondary pyoderma is common with most immune-mediated skin diseases
- Complicates the clinical picture and may be exacerbated with immunosuppressive therapy
- Best to administer antibiotics to determine if lesions improve before or concurrently with immunosuppressive therapy and prior to cutaneous biopsy

Therapy for localized disease – Topical therapy

**Steroid preparations**
- Betamethasone 0.1%, fluocinolone 0.1%, triamcinolone 0.015%, clobetasol 0.05%, mometasone 0.1%, hydrocortisone aceponate spray (Cortavance™ not available in US)
- Apply with gloves or applicator every 24 hrs for 7 days, then taper
- Risk of cutaneous atrophy

**Tacrolimus**
- Macrolide produced by fungus *Streptomyces tsukubaensis*
- Used extensively as an immunosuppressive agent in human transplant patients
- Mechanism of action is similar to cyclosporine, but 10-100x more potent
- Calcineurin inhibitor - suppresses antigen presenting T cells and multiple T cell cytokines, down regulates cytokine expression in other cells and inhibits eosinophil recruitment
- Available in oral, injectable (Prograf®) and topical (Protopic® 0.03 or 0.1%) formulations

**Protopic® 0.1% ointment**
- Efficacy similar to corticosteroids without side effects, however may have mild stinging with application
- Apply every 12 hours for two weeks, then re-evaluate +/- taper
- Wear gloves (FDA black box for cancer risk in humans)
- Expensive!

**Indications**
- Localized discoid lupus erythematosus (DLE), pemphigus erythematosus (PE), pemphigus foliaceus (PF), proliferative thrombovascular necrosis of the pinnae, ischemic dermatopathy, perianal fistulas

Therapy for generalized disease

**Glucocorticoids**
- Indicated for all autoimmune diseases
- Induction dosages in the dog
  - Prednisone 2-4 mg/kg PO every 24 hrs
  - Dexamethasone 0.2-0.4 mg/kg PO every 24 hrs
  - Triamcinolone 0.2-0.6 mg/kg PO every 24 hrs
- Split dose and administer every 12 hours to reduce excessive polyuria and polydipsia
- Induction phase at immunosuppressive dosage for 10-14 days, then taper to every other day, then slowly taper the mg/kg dosage
- Find the minimum dose that keeps the clinical signs in control/remission
  - 0.5-1 mg/kg PO every 48 hrs for prednisone
  - .05-0.1 mg/kg PO every 48-72 hrs for dexamethasone
  - 0.1-0.2 mg/kg PO every 48-72 hrs for triamcinolone
Glucocorticoids - Feline
- Often require nearly double the dose as dogs
- Use prednisolone (not prednisone) - more effective (Graham-Mize et al. Vet Derm 2004)
- If prednisolone is not effective, consider triamcinolone or dexamethasone
  - Triamcinolone 0.4-0.8 mg/kg every 24 hours - maybe steroid of choice in cats
  - Dexamethasone 1 mg/cat PO q 24 hrs

Glucocorticoids – Side effects
- Non-cutaneous
  - Polyuria, polydipsia and polyphagia
  - Panting and behavioral change
  - Muscle atrophy and pendulous abdomen
  - Weight gain
  - Increased risk of occult urinary tract infection
  - Gastrointestinal ulceration, diarrhea and pancreatitis
  - Heart failure (cats)
  - Insulin resistance and diabetes mellitus
  - Adrenal gland suppression (iatrogenic hyperadrenocorticism)
  - Reduced thyroid hormone production
  - Steroid hepatopathy with elevated alkaline phosphatase
- Cutaneous
  - Skin dryness and exfoliation
  - Increased risk of infection (bacterial and fungal) and demodicosis
  - Alopecia (focal and generalized)
  - Comedones
  - Cutaneous atrophy and fragility (especially cats) with delayed wound healing
  - Telangietasia and increased bruising
  - Dermal mineralization (calciosis cutis)
  - “Milia” follicular cysts
  - Atrophic scars

Glucocorticoids - Monitoring
- Close monitoring of body weight
- Regular (every 3 months) re-examinations
- CBC, chemistry, urinalysis and culture every six month; urine culture and sensitivity at minimum

If glucocorticoids alone do not control clinical signs, or side effects are severe, combination immunosuppressive therapy is indicated.

Combination therapy
- Glucocorticoids may be combined with:
  - Cyclosporine, azathioprine (dogs only), mycophenolate mofetil, chlorambucil, leflunomide, tetra/doxycycline and niacinamide, pentoxifylline, intravenous immunoglobulin
- May be initiated at the onset of treatment as many are slow in onset (15-30 days)
- May allow for a lower dose or even discontinuation of glucocorticoids
- Some therapies may potentiate the efficacy of glucocorticoids

Cyclosporine (CsA)
- Polypeptide derived from a Norwegian soil fungus, Tolypocladium inflatum
- Inhibits T lymphocytes, IL-2 and other inflammatory cells and cytokines through targeting intracellular calcineurin
- 5-10 mg/kg PO every 24 hrs
- Slow in onset (4-6 weeks) and must be modified/microemulsified formulation for absorption

Indications
- May be useful for many autoimmune and immune-mediated diseases including pemphigus complex (steroid sparing), cutaneous and systemic lupus erythematosus, ulcerative dermatitis of the collie and Shetland sheepdog, sebaceous adenitis, alopecia areata, sterile nodular panniculitis, perianal fistulas

Side effects
- Immediate side effects: transient vomiting > diarrhea during the first several days of treatment
  - Change habits of administration (full vs. empty stomach), pre-treat with anti-emetic, freeze capsules
- Long term side effects
Gingival hyperplasia, hirsutism and papillomatosis
Occult urinary tract infection
Hepatotoxicity
Opportunistic infections
Lichenoid psoriasiform – like dermatitis
Increased risk of lymphoreticular neoplasia?

- No significant alteration of vital or blood parameters
- Does not interfere with vaccination
- Risk of fatal toxoplasmosis in cats if acute infection acquired during therapy
- Monitoring similar to glucocorticoids
- Whole blood trough levels not always predictive of clinical response
  - 400-600 ng/ml routinely used as therapeutic target

Contraindications
- Age less than 6 months; weight less than 2-3 kg
- Do not use (or use extreme caution) in case of malignancy, pregnant, lactating or breeding animals, liver/kidney disease, FIV/FeLV+
- Do not feed raw meat or allow hunting

Potential pharmacologic interactions
- Drug interactions are due to inhibition or induction of cytochrome P450 enzyme system
- P-glycoprotein substrate - influences deposition and may lead to interactions
- Ketoconazole (increases blood levels of CsA by 30-50%), itraconazole (no significant effect in a recent study), clarithromycin, grapefruit juice, others

Azathioprine
- Purine antimetabolite that interferes with the synthesis of nucleic acids; cytotoxic to T cells
- Use only in dogs; toxicity (myelosuppression) in cats related to reduced thiopurine methyltransferase (TPMT) activity
- 1.5-2.5 mg/kg PO every 24-48 hrs
- Slow in onset (4-8 weeks)
- Side effects
  - Myelosuppression (anemia, lymphopenia, leukopenia and thrombocytopenia)
  - Vomiting and diarrhea (may be severe and hemorrhagic)
  - Hepatotoxicity and pancreatitis

Monitoring
- CBC and chemistry every 2 weeks initially, then every 2-3 months
- Decrease dose or withdraw drug if myelosuppression or hepatotoxicity is evident
- May reinitiate therapy at lower dose once values have normalized

Mycophenolate Mofetil (MMF)
- Inhibits de novo purine (guanosine) synthesis that leads to inhibition of proliferation of lymphocytes and antibody production
- 10 mg/kg PO every 8-12 hours
- Efficacy of 50% when combined with glucocorticoids for PF
- Side effects
  - Diarrhea, weight loss and leukocytosis
    - Increased risk of skin/systemic infections and possibly malignancy
    - Myelosuppression (humans)
  - Fluoroquinolones, metronidazole and cyclosporine may reduce bioavailability (human studies); glucocorticoids may increase metabolism
- Use enteric-coated formulation if used concurrently with proton pump inhibitors
- Do not use in combination with azathioprine
- Monitoring similar to azathioprine, however myelosuppression and hepatotoxicity less common

Chlorambucil
- Nitrogen mustard derivative and alkylating agent that interferes with DNA cross-linking
- 0.1-0.2 mg/kg PO every 24-48 hrs or 2 mg/cat every 48-72 hours
- Often used in cats and small dogs (2 mg sized tablet)
- Side effects
  - Myelosuppression
Vomiting, diarrhea and anorexia

**CBC every 1-2 weeks initially, then monthly, then every 3-6 months**

**Leflunomide**
- Synthetic isoxazole derivative that is metabolized to active metabolite, teriflunomide, and inhibits pyrimidine synthesis; targets B and T cells
- 2-4 mg/kg PO every 24 hours (canine); 10 mg/cat PO q 24 hours (feline)
- Side effects include lethargy, gastrointestinal upset and myelosuppression (leukopenia and thrombocytopenia)
- Used most commonly for cutaneous/systemic histiocytosis and pemphigus foliaceus
- Monitoring similar to azathioprine

**Tetra/doxycycline + Niacinamide**
- Often used as adjunctive therapy (PF) or single agent for PE, DLE and mucocutaneous pyoderma (MMP)
- Tetracycline has anti-inflammatory properties affecting complement activation, antibody production, chemotaxis and prostaglandin synthesis
- Doxycycline: 5 mg/kg PO every 12 hours or 10 mg/kg PO every 24 hours
- Niacinamide inhibits mast cell degranulation and phosphodiesterase
- <10kg body weight: 250 mg PO every 8 hrs
- >10kg body weight: 500 mg PO every 8 hrs
- Slow in onset (1-2 months); once clinical response to observed, frequency may be reduced to once or twice daily
- Effective in 25-65% of cases
- Side effects include vomiting, diarrhea, anorexia and increased liver enzymes (uncommon)

**Pentoxifylline (PTX)**
- Phosphodiesterase inhibitor for oral use
- Xanthine derivative that increases pliability of erythrocytes and decreases blood viscosity
- Decreases fibronectin and production of many cytokines, leukocyte response, T lymphocyte binding to keratinocytes, fibroblast activity and fibrosis (with long term use)

**Indications**
- Vasculitis, ischemic dermatopathy and dermatomyositis
- Proliferative thrombovascular necrosis of the pinnae
- Lupoid onychodystrophy or idiopathic onychomadesis
- Erythema multiforme?
- Other immune-mediated diseases?
- Available in 400 mg controlled release tablet as Trental® vs. generic (variable efficacy?)
- Dose: 15-25 mg/kg PO every 8-12 hours
- Median response time is six weeks (range 4-10 weeks)
- Side effects include possible hyperexcitability, inappetence, vomiting and diarrhea/constipation
  - Use caution with seizure patients, severe renal/hepatic impairment, those at risk for hemorrhage
  - Avoid in patients with retinal or cerebral hemorrhage, intolerance to theophylline

**Human Intravenous Immunoglobulin**
- Sterile, highly purified IgG preparation made from human plasma
- Mechanism of action: blocks and inactivates Fc receptors on macrophages, T and B lymphocytes; eliminates immune complexes, inhibits complement and modulates cytokines
- 1 g/kg IV over 6-12 hours
- Used successfully in a case of erythema multiforme in a cat and toxic epidermal necrosis in a dog
- Risk of acute hypersensitivity and sensitization to human proteins especially with repeated transfusions
- Safety not evaluated, however no adverse side effects reported in dogs or cats

**Sunscreen**
- For cutaneous lupus erythematosus, pemphigus foliaceus and erythematous (depigmenting diseases)
- High SPF (50-80) - Neutrogena Ultra Sheer SPF 85 with helioplex dry touch sunblock or a water repellent sunscreen such as Bullfrog, Epi-Pet™ sun protection
- Will require several repeat applications throughout day

References provided upon request.
Immune-Mediated Skin Diseases: EM, TEN, and More!
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Lecture plan
- Erythema multiforme minor/major (EM)
- Stevens Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Vitiligo
- Uveodermatologic syndrome
- Alopecia areata
- Juvenile cellulitis

EM and SJS/TEN complex
- Diseases characterized by single or massive death (apoptosis) of keratinocytes
- Associated with (viral > bacterial) infections, neoplasia, adverse drug +/- food reactions and idiopathy
  - Herpesvirus and parvovirus
  - Drug related: trimethoprim sulfa, penicillins and cephalosporins
- Different clinical presentations depending on the severity
  - Erythema multiforme minor
  - Erythema multiforme major
  - Stevens Johnson Syndrome
  - Toxic epidermal necrolysis
- Classification schemes are controversial in veterinary medicine

Erythema multiforme
- Uncommon in dogs; rare in cats
- Acute onset of cutaneous inflammatory reaction featuring epidermal apoptosis and lymphocytic satellitosis
- Less frequently associated with adverse drug reactions than SJS/TEN - 19-59% are drug related
- Erythema Multiforme Minor
  - Polycyclic annular erythematous macules and papules that spread peripherally and clear centrally - 38% have classic target lesions
  - Mucosal involvement limited to the oral cavity
  - Persistent urticarial plaques
  - Vesicles, bullae and collarettes
  - May be asymptomatic and self-limiting
- Major
  - Involvement of mucous membranes with extensive vesiculobullous and ulcerative lesions
  - Depression, fever and anorexia
- Distribution of lesions
  - Ventrum (axillae and groin): 65.9%
  - Mucocutaneous junctions: 47.7%
  - Oral cavity: 31.8%
  - Pinae: 25%
  - Footpads: 20.5%
- Nikolsky sign positive: 11.4%
- Pitting edema of distal limbs: 11.4%
- Differential diagnosis
  - Bacterial folliculitis, dermatophytosis, demodicosis, urticaria, eosinophilic dermatitis and other vesicular and pustular disorders
- Diagnosis
  - Clinical signs
  - Cutaneous biopsy and dermatopathology - may be insufficient alone to differentiate between EM/SJS/TEN
- Clinical Management
  - Identify and manage underlying trigger
  - History very important (i.e. drugs, diet)
  - Evaluate for infection and neoplasia
    - PCR on skin for herpes and parvovirus
    - Blood work, urinalysis, abdominal ultrasound and thoracic radiographs
    - If identify and eliminate trigger, clinical signs may resolve within 3 weeks
  - Supportive care, analgesics, immunosuppressive therapy, IV IgG and pentoxifylline may be of benefit

**Toxic epidermal necrolysis (TEN)**
- Rare, life-threatening, extensive vesiculobullous and ulcerative disorder of skin and oral mucosa of dogs and cats
- More severe form of SJS
- Most cases associated with adverse drug reactions including topical therapy (flea dips) and vaccines > neoplasia, infections pregnancy and idiopathy
- Acute onset of pyrexia, anorexia, lethargy and depression
- Multifocal to generalized erythematous macules involving skin and multiple mucosal surfaces (oral and footpads) rapidly progresses to necrotic and ulcerative lesions
- Nikolsky sign positive
- Differential diagnosis
  - Burns, severe EM, superficial suppurative necrolytic dermatitis, toxic shock syndrome and vasculitis
- Diagnosis
  - Acute progressive history of skin lesions
  - Clinical signs
  - Cutaneous biopsy and dermatopathology
- Clinical Management
  - Mortality rate of 30-50% in humans - greatest in idiopathic cases
  - Guarded to poor prognosis in animals
  - Manage similar to massive second degree burn patient
  - Discontinue any suspected drug
  - Manage ulcers and wounds to avoid infection and sepsis
  - Address fluid, electrolyte and colloid losses
  - Analgesia
  - Use of glucocorticoids is controversial
  - Cyclosporine, IV IgG, plasmapheresis, IV IgG, anti-TNFα antibodies and N-acetylcysteine used in human disease

**Vitiligo**
- Acquired disease associated with melanocyte destruction resulting in leukoderma and/or leukotrichia
- Uncommon in dogs; rare in cats
- Pathogenesis - probably immune-mediated
  - Anti-melanocyte antibodies found in humans, dogs and cats
  - Multi-factorial pathogenesis
  - May be hereditary in Belgian tervuren, rottweiler and old English sheep dog
  - Breed predisposition for German shepherd, collie, doberman, giant schnauzer, Newfoundland, boxer and Siamese cat
- Clinical Signs
  - Young adult animals
  - Macular leukoderma and leukotrichia
  - Nose, lips, buccal mucosa, facial skin, footpads, claws, coat and genital mucosa
  - May repigment or progress
- Diagnosis and Treatment
  - History and clinical appearance
  - Histopathology: normal epidermis and dermis, absent melanocytes, and inflammation (interface) only in early stages
- Treatment
- Benign neglect – cosmetic disease and may spontaneously improve
- L-phenylalanine 50 mg/kg QD for > 6 months (precursor of L-tyrosine)

**Uveodermatologic syndrome**
- Rare syndrome of concurrent granulomatous uveitis and depigmenting dermatitis in dogs
- Ocular signs are often the presenting problem and may be severe: granulomatous uveitis leads to irreversible blindness
- Dermatologic signs: depigmentation and ulceration
- Similar to the Vogt-Koyanagi-Harada syndrome in humans
  - Cell-mediated hypersensitivity against melanocytes
- **Epidemiology**
  - Breed predisposition for Akita (with genetic basis), Alaskan malamute, Australian shepherd, basset hound, dachshund, chow, Samoyed and Siberian husky
  - Also recognized in several other breeds
  - Young to middle aged dogs
- **Dermatologic changes**
  - Follow ocular changes
  - Depigmentation +/- mild erythema and scale of nose, lips, eyelids, footpads, genitalia and hair (poliosis)
  - Alopecia of dorsal muzzle
  - Erosions, ulcerations and crusts of lips, nose and footpads
- **Differential diagnosis**
  - Autoimmune dermatoses (cutaneous lupus, pemphigus)
  - Vitiligo
  - Epitheliotropic lymphoma
  - Mucocutaneous pyoderma (MCP)
  - Leishmaniosis (may have uveitis)
- **Diagnosis**
  - Clinical appearance
  - Consistent ophthalmic lesions
  - Exclusion of other diseases
    - ANA (may be positive)
    - Coombs’ test
    - Rheumatoid factor
    - Leishmania testing
    - Cytology (MCP vs. pemphigus)
    - Cutaneous biopsy: superficial band-like (lichenoid) infiltrate of macrophages with large histiocytes, lack of apoptosis of the basal epidermal layers (≠ lupus) and pigmentary incontinence
- **Treatment**
  - Early and aggressive ocular therapy is mandatory - consult an ophthalmologist!
  - Therapy for cutaneous lesions
    - Benign neglect if lesions are mild (only depigmentation)
    - Systemic immunosuppressive therapy if severe
  - Similar to other autoimmune dermatoses
  - Leukotrichia may persist

**Alopecia areata**
- Uncommon or infrequently recognized disease of dogs; rare in cats
- Characterized by patches of non-scarring non-inflammatory alopecia
- GSD, dachshund, beagles and pinschers may be predisposed
- Median age is 5 years (range 1-11 yrs)
- **Pathogenesis**
  - Immune-mediated destruction of follicles
  - Autoantibodies vs. trichohyalin, inner root sheath, keratins and hair matrix Ag
  - Suppressive CD8+ lymphocytes in the hair bulb (AA) or in the isthmic wall (pseudopelade)
  - CD1+ dendritic antigen-presenting cells and CD4+ and CD8+ lymphocytes in the perifollicular dermis
• Clinical signs
  o Progressive patchy to diffuse alopecia especially on the head and face
  o Skin has normal appearance
  o Hair may regrow spontaneously and be lighter in color

• Differential diagnosis
  o Folliculitis
  o Traction alopecia
  o Topical steroid reaction
  o Follicular dysplasia
  o Pseudopelade
  o Endocrine alopecia

• Diagnosis
  o Clinical signs
  o Exclusion of other causes of alopecia
  o Trichoscopy - “exclamation point” roots
  o Histopathology: lymphocytes, histiocytes and plasma cells accumulate in the perifollicular dermis, lymphocytes infiltrate the bulb, apoptosis of bulbar keratinocytes, follicular atrophy with dysplastic hair shafts, orphaned glands and arrector pili muscles

• Treatment
  o Benign neglect - 60% may have spontaneous and complete hair re-growth
  o Cyclosporine 5mg/kg PO q 24 hours
  o Glucocorticoids at immunosuppressive doses for more severe or generalized cases

Juvenile cellulitis
• “-Pupple strangles”
• -Uncommon granulomatous and pustular disorder of face, pinnae and submandibular lymph nodes
• -Age of onset between 3 weeks-4 months
• -Golden retrievers, dachshunds and Gordon setters may be predisposed
• -Clinical Signs
  o -Edema  pustules, furunculosis and purulent exudate
  o -Otitis externa with edematous pinnae
  o -Rarely associated with sterile panniculitis or arthritis
  o -Systemic signs: lethargy and depression (fever often absent)

• Diagnosis
  o Signalment, history and clinical signs
  o Histopathology: multifocal discrete or confluent granulomas and pyogranulomas consisting of clusters of large epithelioid macrophages with cores or neutrophils; sebaceous and epidermal glands are often obliterated
  o Response to treatment

• Treatment
  o Early and aggressive treatment to avoid severe scarring
  o Prednisone 1-2mg/kg PO q 12 hours for 2 weeks, then every 48 hours for 2 weeks, then taper
  o Dexamethasone 0.2 mg/kg PO q 24 hours
  o Cyclosporine 5-7 mg/kg PO q 24 hours
  o Griseofulvin 14.2-34 mg/kg PO q 12 hours for 3 weeks, then taper
  o Manage secondary infection concurrently

References provided upon request.
Lecture Plan

- Definition and classification
- Cause and pathogenesis
- Clinical presentation
- Infectious, immune-mediated, hereditary and idiopathic vasculitides
- Dermatomyositis
- Diagnosis
- Clinical management

Definition

- Vasculitis: inflammation and damage to the vessel wall
  - Inflammatory cells within the vessel wall
  - Edema of the endothelium
  - Cell rich lesions
- Vasculopathy: alteration of vessels with absence of inflammatory infiltrated
  - Ischemic lesions of tissues (ischemic dermatopathy)
  - Cell poor lesions

Classification

- Clinical – etiologic
  - Infectious
  - Immune-mediated
  - Hereditary and idiopathic
- Pathologic – type of inflammatory infiltrate
  - Neutrophilic (acute)
  - Lymphocytic (chronic)
  - Granulomatous (uncommon)

Cause and pathogenesis

- Not a definitive diagnosis, but a cutaneous reaction pattern associated with multiple causes or diseases
- Usually immunologically mediated and the result of a drug reaction or infection
- Uncommon in dogs; rare in cats
- Any age, breed or sex may be affected

Clinical presentation

- Skin lesions may precede development of other organ disease
- Often occur on dependent areas of the body, over areas of pressure and extremities
  - Lower legs, elbows, groin, scrotum, pinnae, tip of tail, footpads, claws and lips (+/- oral mucosa)

Cutaneous signs

- Acute or severe vasculitis
  - Pulpable purpura, erythematous plaques, hemorrhagic bullae, eschars, crateriform ulcers and pitting edema
  - Erythematous urticaria, papules, pustules and nodules
- Ischemic dermatopathy (with chronicity)
  - Results from loss of blood supply
  - Scarring alopecia, shiny scaly skin, atrophy and comedones

Extracutaneous signs

- Polyarthropathy, myopathy, neuropathy, hepatopathy, thrombocytopenia and anemia
- Anorexia, depression and pyrexia may be present
Vasculitis – Infectious causes
- Sarcocystis and rickettsial diseases
  - Localization in the endothelium
- Babesia, Ehrlichia/Anaplasma, Bartonella
  - Localization in or near erythrocytes
- Leishmania
  - Immune-complex deposition
- Bacterial septicemia (especially gram negative), endotoxemia and disseminated intravascular coagulation (DIC)

Vasculitis – Immune-mediated causes
- Cutaneous drug eruption
- Systemic lupus erythematosus
- Dermatomyositis
- Adverse reaction to food

Immunologic reactions - Mechanisms of hypersensitivity
- Type III – immune complexes
  - Deposition of immune complexes in vessel walls and filtering membranes leads to complement activation
- Type III – immune complexes
  - First exposure has a latency of 6 days minimum for antibody production; second exposure results in more rapid development of clinical signs
  - Penicillins, sulphonamides and itraconazole

Focal cutaneous vasculitis
- Associated with rabies vaccination
- Poodles, Yorkshire terriers and silky terriers may be predisposed
- Annular area of variable alopecia, hyperpigmentation +/- scaling and erythema overlying indurated tissue
- Caudal lateral thigh > shoulders
- Appear 2-6 months after injection; persist for months to years
- Lesions at distant sites may develop resulting in ischemic dermatopathy

Hereditary and idiopathic vasculitides
- Proliferative arteritis of the nasal philtrum of the St. Bernard
- Proliferative thrombovascular necrosis of the pinnae
- Familial cutaneous vasculitis of German shepherd dogs (GSD) and Jack Russell terrier
- Cutaneous and renal glomerular vasculopathy

Proliferative arteritis of the nasal philtrum
- Also described in giant schnauzer, basset hound, Doberman pinscher, Labrador retriever, Newfoundland and Samoyed
- Young dogs: 2-6 years
- Limited to nasal philtrum
- Well demarcated linear to oval ulcer with long axis parallel to the lip
- Intermittent episodes of severe epistaxis

Proliferative thrombovascular necrosis of the pinnae
- Described in dogs only
- No age, breed or sex predilections
- Lesions begin on apical margins and spread along concave aspects
- Elongated necrotic ulcer at center of lesions with thickened hyperpigmented zone and scale/crust in periphery

Familial cutaneous vasculitis of GSD
- Autosomal recessive trait
- Young puppies (usually by 7 weeks of age)
- Alopecia, crusts and ulceration with edematous depigmented foot pads
  - Pinnae, nasal planum and tail
• Nodular dermatitis, collagenolysis, vascular degeneration, cell poor interface dermatitis and basal cell apoptosis on histopathology
• Role of vaccines?

**Cutaneous and renal glomerular vasculopathy**
- “Alabama rot” or “Greenetrack disease”
- Kenneled and racing greyhounds
- Young to middle aged dogs (6 months-6 years)
- Palpable purpura with pinpoint-10 cm lesions that rapidly become dark/black leading to deep ulcers within 1-2 days +/- pitting edema
  o Limbs, groin and trunk
- Variable pyrexia, lethargy, polydipsia, polyuria, vomiting, tarry stools and renal failure
- May be associated with verotoxin (Shiga-like toxin) produced by *E. coli* from consumption of contaminated raw meat

**Dermatomyositis**
- Hereditary idiopathic inflammatory condition of skin and muscles
- Collie, Shetland sheepdog, Beauceron shepherds, Belgian Tervurens and Portuguese water dogs
- Observed in other breeds and mongrels
- No sex predisposition
- Familiar autosomal dominant mode of inheritance (collies and Shelties)

**Clinical presentation – cutaneous signs**
- First clinical signs at 7-11 weeks to 3-6 months of age
- Extent of skin lesions evident at 1 year
- Alopecia, erythema, scaling, mild crust and ulcers
  o Face, periocular areas, muzzle, pinnae, carpal/tarsal regions, digits and tip of tail
  o Claw abnormalities

**Extracutaneous signs**
- Myositis occurs months after skin lesions and correlates with severity
- Asymptomatic atrophy (common)
- Muscle atrophy particularly of the head
- Difficulties with prehension and chewing
- Megaesophagus
- Weakness and stiff gait

**Pathogenesis**
- Etiology unknown
- High levels of circulating immune-complexes; concentration correlates with the severity of the lesions
- Deposition of immune-complexes in the filtering membranes creates Arthus hypersensitivity type III reaction
- Vessel destruction by complement
- Exacerbation with trauma, UV light and stress (pregnancy, parturition, lactation)

**Diagnosis**
- Differential diagnoses include folliculitis, discoid lupus erythematosus, epidermal bullosa simplex and other causes of vasculitis
- History, examination findings, cutaneous +/- muscle biopsy, EMG and laboratory testing to rule out other conditions

**Histopathology**
- Cell poor vasculopathy with atrophy of adnexa and discrete dermo-epidermal clefting

**Vasculitis – Differential diagnoses**
- Classic lesions resembling ecchymosis or petechia
  o Coagulopathy, erythema multiforme, systemic lupus erythematosus, cold agglutinin disease, frost bite, DIC and lymphoreticular neoplasia
- Acute necrotic and ulcerative lesions
Subepidermal bullous diseases, burns and deep pyoderma
- Urticarial lesion
  - Hypersensitivity disorders

Vasculitis - diagnosis
- Try to determine and manage underlying cause!
- Drug, vaccine and travel history
- Source of septic vasculitis such as deep pyoderma, cellulitis, endocarditis
- PCR or antibody testing for vector borne diseases
- Cutaneous biopsy and histopathology
- Histopathology will be influenced by
  - Vascular syndrome
  - Age of lesion biopsied relative to vascular damage
  - Secondary infections
- Important to provide description of lesions and differential diagnoses to pathologist
- D-dimers
  - Measures fibrin degradation products
  - Positive (> 500 ng/ml) in dogs with thrombi
- Fibrinogen levels?

Clinical management
- Clinical course depends on the vascular syndrome present
- Prognosis depends on extent of internal organ involvement and underlying or precipitating factor (if identified)
- Manage any infectious cause
- Immunomodulatory therapy

Focal or localized cutaneous vasculitis
- Surgical excision
- Pentoxifylline 22-35 mg/kg PO q 8-12 hours
- Vitamin E 200-800 IU PO q 12 hours
- Tacrolimus 0.1% ointment topically q 12 hours x 14 days, then re-evaluate
- Discontinue rabies vaccination when possible to avoid more widespread lesions upon repeated injections

Generalized vasculitis
- Pentoxifylline and vitamin E PO
- Doxycycline and niacinamide PO
- Immunosuppressive therapies – glucocorticoids, cyclosporine and azathioprine
- Sulphones – dapsone and sulfasalazine

References provided upon request.
More than Warts:
Viral Diseases of the Skin
Jeanne Budgin, DVM, DACVD
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- CAPSOMERE, a subunit of the capsid, contains nucleic acid (DNA, RNA) >> self assemble to form CAPSID, outer covering of protein that encloses and protects genetic material
- CAPSOMERE + CAPSID = NUCLEOCAPSID
- Envelope = lipid material that surrounds the nucleocapsid
- Variable shape: cubic, bullet shaped, filamentous, helical and complex; icosahedral (herpes virus) most common

Infection - Transmission
- Vectors (insect, tick bites), skin wounds, mucous membranes
- Primary replication at the site of inoculation +/- secondary dissemination by direct contact with adjacent tissues and via bloodstream (viremia)

Feline and canine viral diseases
- Uncommon and under diagnosed
- Cause direct skin damage, induce immunosuppression and secondary infections, cause or associated with neoplasia

Feline viral diseases
- Feline leukemia and feline immunodeficiency viruses
- Cowpox virus
- Feline corona virus (feline infectious peritonitis)
- Herpes and calici viruses
- Papilloma virus

Feline leukemia virus (FeLV)
- Immunosuppressive oncogenic retrovirus
- Affects skin by cytosuppressive effect
  - Gingivitis, pyoderma (folliculitis), abscess, paronychia, poor wound healing, seborrhea, exfoliative dermatitis, cutaneous horns, giant cell dermatosis and generalized pruritus
  - Increased susceptibility to dermatophytosis, demodicosis, Malassezia dermatitis
- Cause of lymphoma and fibrosarcoma (indirectly via FeSV)

FeLV-Associated Cutaneous Horns
- Conical or cylindrical masses of acellular keratin on foot pads > nasal planum, eyelids

FeLV-Associated Giant Cell Dermatosis
- Rare pruritic crusting dermatitis
- Scaly, erose, crusted lesions over lips, face, head, pinnae and preauricular skin > feet/footpads and mucocutaneous junctions

Diagnosis
- ELISA, IFA
- Histopathology +/- IHC: epidermal hyperplasia with syncytial giant cells and apoptosis

Therapy
- Antibiotics and antifungal therapy for secondary infections
- Human recombinant alpha-2b interferon or feline omega interferon PO or subcutaneously (protocols vary)
- Surgical removal (horns)
- Confine to indoors

Feline immunodeficiency virus (FIV)
- Immunosuppressive retrovirus
- Often co-infection with FeLV
- Chronic/recurrent infection - pyoderma, abscess, otitis, gingivitis and stomatitis
- Predisposition to development of demodicosis, notoedric mange, dermatophytosis, candidiasis, Cryptococcosis and other infections
- Increased risk for leukemia/lymphoma (B cell), fibrosarcoma, squamous cell carcinoma and mast cell tumors
**Diagnosis**
- ELISA, Western blot

**Therapy**
- Antibiotics as needed
- Human recombinant alpha-2b interferon or feline omega interferon PO or subcutaneously (protocols vary)

**Feline cowpox virus**
- Epiteliotropic DNA orthopoxvirus reported in United Kingdom and continental Europe
- Wild rodents (reservoir of disease) and contracted via direct inoculation (bites, scratches)
- Ulcerated nodule on head, neck or forelimb
- Viremic phase +/- systemic signs leads to dissemination and new lesions: papules/nodules, ulcers and crusts, oral vesicles/ulcers (20% of cats), pulmonary involvement and death (rare)

**Diagnosis**
- Clinical presentation
- Serology, viral isolation and PCR
- Histopathology: hyperplasia, ballooning degeneration, microvesicle formation and necrosis of epidermis and outer root sheath with eosinophilic intracytoplasmic inclusion bodies in epidermis, hair follicles and sebaceous glands

**Therapy**
- Spontaneous resolution in 3-4 weeks
- Treatment of secondary infections and supportive care
- Glucocorticoids are contraindicated
- Possible zoonosis!

**Feline infectious peritonitis (FIP)**
- Systemic viral disease caused by stains of coronaviruses (FCoV)
- Multiple non-pruritic erythematous papules and nodules over neck, forelimbs and thorax reported in two cases with concurrent clinical signs of FIP
- Histopathology: mid to deep dermal pyogranulomatous infiltrate, phlebitis, dermal necrosis and hemorrhage, FCoV antigen positive within macrophages

**Feline rhinotracheitis**
- Double stranded DNA α-herpesvirus-1 that infects the upper respiratory tract
- Oral, corneal and cutaneous ulceration
  - Adult cats
  - Ulcerative-necrotic facial dermatitis; similar lesions in other areas including foot pads
  - Exfoliative erythema multiforme reported following upper respiratory infection

**Diagnosis**
- History and clinical presentation
- Immunohistochemistry, viral isolation and PCR
- Histopathology: intense tissue eosinophilia, nuclear inclusion bodies in keratinocytes and necrosis of follicular and glandular epithelium

**Therapy**
- Antibiotics for secondary infection
- Famciclovir 40-90 mg/kg every 8 hours
- Human recombinant alpha-2b interferon or feline omega interferon PO or subcutaneously (protocols vary)
- Lysine 250-500 mg cat/day PO every 12 hours (questionable efficacy)
- Imiquimod 5% cream once daily for 3 days, then three times per week or every 48-72 hours
- Topical acyclovir 5% cream (Zovirax)
- Limit stress and glucocorticoid use to avoid relapses

**Feline calicivirus (FCV)**
- Small single stranded RNA virus with many strains
- Primarily infects the oral cavity and pharynx but may disseminate
- Spread via direct contact with ocular, nasal and oral secretions
- 20-30% have persistent tonsillar and oropharyngeal infections and shed virus intermittently

**Clinical signs**
- Oral > nasal vesicles and ulcers; edema and ulceration of the feet (“paw and mouth disease”)
- Concurrent depression, pyrexia, sneezing and conjunctivitis; gingivitis and stomatitis with chronic infection
- Immune-mediated arthropathies (rare)
• Virulent systemic FCV infection (vsFCV)
  o Adult cats more susceptible
  o Facial and paw edema, ulcers and crusting of oral cavity, nose, lips, pinnae, periocular region and distal limbs
  o Pyrexia with ocular and nasal discharge
  o Icterus and hemorrhagic diarrhea, pneumonia, pancreatitis and pericarditis
  o Mortality rate of 30-50%

**Diagnosis**

- Clinical signs
- Viral isolation, PCR, IHC and fluorescent antibody testing on oropharyngeal or conjunctival swabs
- Histopathology: ulceration and epidermal necrosis with ballooning degeneration of keratinocytes and epithelial cells, dermal edema and vasculitis

**Feline papillomavirus**

- Four disease syndromes: (1) feline cutaneous papillomas; (2) cutaneous fibropapilloma or sarcoids; (3) viral plaques; (4) feline bowenoid in situ carcinoma and cutaneous invasive squamous cell carcinoma

**Cutaneous papillomas**

- Originally reported in Persian cats (1990)
- Multiple hyperkeratotic and hyperpigmented plaques of variable size on trunk
- May be associated with immunosuppression
- Papillomavirus antigen FdPV-21 (IHC)

**Feline cutaneous fibropapillomas**

- Also called feline sarcoïds due to resemblance to equine sarcoïds
- Nodular to pedunculated exophytic often ulcerated masses located on nose, lips, head, neck, digits and tip of tail
- Young often outdoor cats (< 5 yrs of age)
- Majority of lesions are positive for papillomavirus with strong similarity to bovine papillomavirus 1 (PCR)

**Feline viral plaques**

- Multiple ovoid to elongated slightly raised and irregular +/- hyperpigmented lesions that are less than 8 mm in length
- Older cats (7 months – 15 years)
- Often associated with FIV, FIP or chronic glucocorticoid therapy
- Intraleosional Demodex mites and possible malignant transformation

**Feline bowenoid in situ carcinoma**

- Multicentric squamous cell carcinoma in situ
- Associated with multiple types of papillomaviruses
- Melanotic macules, hyperkeratotic, seborrheic plaques

**Diagnosis**

- Immunohistochemistry, IHC and PCR
- Histopathology: hyperplasia and dysplasia of the epidermis, koilocytosis and intracytoplasmic inclusion bodies

**Therapy**

- Surgical excision when possible
- Gamma-radiation (strontium-90 pleiotherapy) may be successful, but does not inhibit the development of new lesions
- Interferon PO or subcutaneously
- Imiquimod 5% cream for localized lesions

**Canine viral diseases**

- Canine papillomavirus
- Distemper

**Canine papillomavirus**

- Seven subtypes of papillomaviruses identified in dogs
- Transmitted by direct or indirect (fomite) contact
- At least 5 clinical presentations: (1) oral papillomatosis; (2) cutaneous papillomatosis in the adult dog; (3) inverted papilloma; (4) multiple pigmented plaques; (5) pedal papillomatosis

**Oral papillomatosis**

- Transmitted by direct contact
- Usually in young/immunocompromised dogs with incubation period of at least 1 month
- Typical verrucous white/grey lesions on mucous membranes may be observed in combination with cutaneous lesions
- May hinder prehension and mastication of food
**Diagnosis**

- Clinical Signs
- Histopathology +/- IHC: squamous papillomas characterized by papillated (exophytic) epidermal hyperplasia with variable degrees of ballooning degeneration (koilocytosis), giant, clumped pleomorphic keratohyaline granules and basophilic intranuclear inclusion bodies (variable finding)
- Often spontaneous regression in healthy animals within 3 months

**Cutaneous papillomatosis**

- Lesions similar to oral papillomatosis
- Older animals; male > female
- Increased incidence in Cocker spaniel and Kerry blue terrier
- Lesions on the skin (head, eyelids, feet) and oral mucosa
- May not regress spontaneously
- Related to immunosuppression and cyclosporine therapy

**Inverted papilloma**

- Usually young dogs - 8 months to 3 yrs of age
- Nodular raised firm lesions with central pore on abdomen or groin
- Probably a different papilloma subtype

**Multiple pigmented plaques**

- Young dogs - 2-4 yrs of age
- Pug, miniature schnauzer and Chinese Shar Pei may be predisposed
- Melanotic macules and plaques, increased scale and hyperkeratosis on ventral body areas
- Association with immunosuppression
- Similar to verruciform epidermal dysplasia of humans and may progress to squamous cell carcinoma in situ

**Pedal papillomatosis**

- Described on multiple foot pads of young animals as firm, hyperkeratotic and horn-like that may be painful and cause lameness
- Very similar to viral papillomas histologically, but not confirmed to be caused by virus

**Therapy**

- Focal or locally extensive lesions in young dogs (< 2 years of age)
  - Benign observation
  - Surgically excise/crush – stimulates local cell immunity?
  - Topical imiquimod 5% cream ($$) or retinoids ($$) for inverted papillomas
  - Isolate from other dogs
- More severe lesions in adult dog (> 2 years of age)
  - Surgical excision (cryo, laser or sharp)
  - Azithromycin 10mg/kg PO every 24 hours x 14 days, cimetidine 10 mg/kg PO every 8-12 hrs, interferon α-2b at 20,000 IU PO every 24 hrs x 6-8 weeks
  - Autogenous or commercially available wart vaccines
  - Homeopathic thuja, oral zinc, vitamin E and immune support
  - Monitor for malignant transformation

**Distemper**

- Infection by paramyxovirus (RNA virus)
- Widespread small papules and pustules on the abdomen (impetigo)
- Nasal pad and foot pad hyperkeratosis (“hard pad” disease); flat, thin and hard in center of pad with peripheral hyperkeratosis

**Diagnosis**

- Immunohistochemistry and PCR
- Histopathology: marked orthokeratotic and parakeratotic hyperkeratosis, acidophilic/eosinophilic intracytoplasmic inclusion bodies within keratinocytes with occasional multinucleated syncytial giant cells in epidermis

References provided upon request.
Case 1 – “Kitty”
- 5 year old FS DSH
- 2 month history of moderately pruritic crusting dermatosis of facial area, pinnae, ventrum, digits and nail beds
- Decreased appetite with weight loss (1 ½ lbs) also reported

List six differentials:
What diagnostics are indicated?

Results
- Skin cytology (impression smear beneath crust): full fields of intact neutrophils with mild erythrocytes and acantholytic cells
- Skin scraping: negative
- Wood’s lamp: negative; fungal culture (DTM): pending
- Dermatopathology: subcorneal and outer root sheath pustules containing neutrophils, acantholytic cells, and fewer numbers of eosinophils
- Blood work and urinalysis: within normal limits, except mild neutrophilia

What is the diagnosis?
Treatment and follow up
- Triamcinolone at 0.5 mg/kg PO every 24 hours
- Lesions improved within one week and resolved within three weeks
- Appetite improved and body weight stabilized
- Therapy was slowly tapered over several weeks, but patient relapsed when discontinued
- Long-term maintenance on lowest dose possible to control clinical signs (0.15 mg/kg PO twice weekly)

Pemphigus foliaceus
- Transient, often symmetrical, pustules with crust, scale, alopecia and erosions of dorsal nasal planum, periocular areas, pinnae, footpads and claw folds
- Most common immune-mediated dermatosis of cats
- Pathogenesis involves targeting of adhesion molecules on keratinocytes

Signalment and clinical signs
- Domestic short-haired cats over represented; no sex predisposition, median age of onset 5 yrs. (range < 1 yr – 17 yrs)
- Mild-severe pruritus, lethargy, fever, anorexia, weight loss and lymphadenopathy may be present

Diagnosis and treatment
- Skin biopsy 6 mm (3-4); steroid withdrawal recommended to increase diagnostic yield
- Treatment with immunosuppressive therapy - oral triamcinolone may be most effective with fewer adverse effects
- Addition of cyclosporine may provide steroid sparing effect
- Changes in treatment protocol often required

Case 2 – “Rudy”
- 8 month old MN DSH from cat rescue organization
- 3 month history of a mildly pruritic, ulcerative lesion limited to the dorsal nasal planum
- Previous histopathology was consistent with eosinophilic granuloma, but limited response to oral prednisolone

List eight differentials:
What diagnostics are indicated?

Results
- Skin cytology (impression smear beneath crust): mixed neutrophils and eosinophils with moderate intracellular and extracellular cocci bacteria; add on aerobic culture: pending
- Skin scraping: negative
- Wood’s lamp: negative; fungal culture (DTM): pending.
- Dermatopathology: severe eosinophilic dermatitis with ulceration of epidermis and embedded cocci bacteria
- Immunohistochemistry: positive for herpes virus in dermis and epidermis
What is the diagnosis?

Treatment and follow up

- Famciclovir at 45 mg/kg PO every 12 hrs - initial improvement over several weeks, followed by severe relapse and poor response to increased dose
- L-lysine at 250 mg PO every 12 hrs
- Doxycycline at 5 mg/kg PO every 12 hrs for six weeks (based on culture)
- Topical acyclovir (Zorivax) every 12 hours - discontinued shortly after due to irritation
- Surgical excision

Feline herpes virus associated dermatitis

- Variable pruritic ulcerative lesions on rostral muzzle, nasal planum, periocular area, oral cavity +/- limbs
- More common in overcrowded, multi-cat environments
- May have concurrent ocular and respiratory disease

Diagnosis

- Skin biopsy: severe eosinophilic dermatitis with necrosis of epidermis and follicular epithelium +/- viral inclusion bodies in surface and adnexal epithelium (often misdiagnosed as eosinophilic granuloma complex)
- Perform IHC or PCR if no inclusion bodies present

Treatment

- Famciclovir at 45-90 mg/kg PO every 8 hrs
- Topical acyclovir (Zovirax) every 8-12 hrs or imiquimod (Aldara) 3x week
- L-lysine at 250-500 mg PO every 12 hrs (questionable efficacy)
- Oral or SQ IFN-α or perilesional/SQ rFeIFN-ω (protocols vary)
- Relapse common

Case 3 – “Olivia”

- 10 month old FS DSH
- Unknown duration of thin skin that “tears easily” without excessive bleeding. Mildly pruritic.
- Dermatological examination: multifocal linear ulcerations and cicatrices in pericervical area with subjective increased in elasticity and extensibility

List eight differentials

What diagnostics are indicated?

Results

- Skin extensibility index: 20%
- Dermatopathology: non-diagnostic
- Flea combing: positive for flea feces
- Blood work and urinalysis: within normal limits

What is the diagnosis?

Treatment and follow up

- No specific treatment is indicated
- Avoid trauma - treat and prevent fleas and other causes of pruritus, maintain indoors and away from other animals, remove sharp or rough objects/edges from environment, declaw or apply Soft paws

Ehlers-Danlos syndrome

- Group of inherited collagenopathies characterized by defective collagen synthesis or fiber formation that results in abnormal skin extensibility and fragility
- Dermal collagen may appear normal or be fragmented, disoriented and abnormally organized (EM may be useful in diagnosis)
- Guarded prognosis

Case 4 – “Rufus”

- 8 year old MN Siamese cross
- 2 month duration of skin lesions that began as mild non-pruritic erythema and scale of head and pinnae and progressed to more generalized, intensely pruritic, alopecic lesions with heavy scale (exfoliative dermatitis)

List six differentials

What diagnostics are indicated?

Results

- Skin cytology (acetate tape prep): 0-1 keratinocytes/oif, 2+ Malassezia yeast
- Deep skin scraping: negative
- Wood’s lamp: negative; fungal (DTM): pending.
- Dermatopathology: Severe hyperkeratosis with multifocal keratinocyte necrosis; mild pleocellular infiltrate in dermis which focally obscures dermoeipidermal junction (interface dermatitis)
- Blood work and urinalysis: within normal limits

**What additional diagnostic test is indicated?**

**What is the diagnosis?**

**Treatment and follow up**
- Fluconazole at 5 mg/kg PO every 24 hrs x 30 days resulted in resolution of pruritus and Malassezia yeast based on repeat cytology
- Complete surgical excision was performed and histopathology was consistent with thymoma
- Skin lesions dramatically improved 4 months after surgery; resolved with no recurrence at 6 months post-operatively

**Thymoma-associated exfoliative dermatitis**
- Paraneoplastic exfoliative dermatitis
- Diffuse erythema of skin accompanied by exfoliation and scaling
- Pruritus is not a feature; but Malassezia overgrowth may contribute
- Specific histopathologic changes
- Surgical resection of thymoma is treatment of choice

**Case 5 – “Minerva”**
- 7 year old MN Maine Coon
- 2 month history of non-pruritic ulcerative lesion on neck
- No improvement with previous injection of methylprednisolone acetate

**List Seven Differentials:**
**What Diagnostics Are Indicated?**

**Results**
- Skin cytology (impression smear from surface): mild degenerate neutrophils with intra and extracellular cocci bacteria
- Deep skin scraping and trichogram: negative
- Wood’s lamp and DTM: negative
- Dermatopathology: extensive epidermal ulceration and superficial dermal necrosis with minimal to mild dermal inflammation

**What is the diagnosis?**

**Treatment and Follow Up**
- Marbofloxacin at 12.5 mg/cat PO every 24 hrs x 30 days - prescribed at presentation with mild improvement
- Topical 1% silver sulfadiazine cream was ineffective
- Surgical excision was planned with primary veterinarian

**Idiopathic Ulcerative Dermatosis**
- Unknown etiology
- Occurs most commonly on dorsal midline of caudal cervical or interscapular area
- Pain +/- pruritus +/- peripheral lymphadenopathy
- Subepidermal band of dermal fibrosis may be present in chronic lesions

**Treatment**
- Identify and manage underlying cause
- Consider lime sulfur trial for *Demodex gatoi* (especially if pruritic)
- Glucocorticoids often ineffective
- Analgesics with oft bandage or creative barrier, Soft paws for healing if pruritic
- Prognosis is guarded to poor

**Case 6 – “Sophie”**
- 8 year old FS DSH
- Six month history of pruritic well circumscribed, erythematous, erosive plaque on ventral abdomen
- History of well controlled diabetes mellitus

**List three differentials**
**What diagnostics are indicated?**

**Results**
- Skin cytology (impression smear from surface): moderate neutrophils (often degenerate) with mild intracellular and extracellular cocci bacteria; 5-7 eosinophils/otf
Flea combing: negative  
Dermatopathology: hyperplastic, superficial and deep perivascular to diffuse eosinophilic dermatitis

**What is the diagnosis?**

**Treatment and follow up**
- Revolution (selamectin) every 4 weeks  
- Simplicef (cefopodoxime) at 10 mg/kg PO every 24 hours - resulted in near resolution of lesion, but only mild reduction in pruritus  
- Atopica (cyclosporine, CSA) 7 mg/kg PO every 24 hours for six weeks, then discontinued  
- Food elimination dietary with Royal Canin rabbit and pea for 8 weeks - no sustained improvement documented on diet alone  
- Intradermal skin and blood allergy performed and immunotherapy (IT) initiated  
- Managed on IT alone with no pruritus or recurrence of lesion

**Feline eosinophilic plaque**
- Siamese breed over-represented  
- Single or multiple well circumscribed, raised, round, erythematous, often moist and eroded, intensely pruritic lesions on abdomen, inguinal region, medial thighs > neck, mucocutaneous junctions  
- +/- Peripheral lymphadenopathy  
- Tissue and blood usually present

**Treatment**
- Parasite control: Revolution (selamectin) every 2-4 weeks, Advantage (imidacloprid) every 2-4 weeks, Comforts (spinosad) PO every 4 weeks, Capstar (nitempyram) every 48 hours  
- Antibiotics for minimum of 4 weeks - always attempt prior to steroids or cyclosporine  
- Manage underlying allergy  
- In relapsing or refractory cases, steroid or CSA therapy often best option

References provided upon request.
What’s New in the Management of Dermatophytosis?
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Etiology
- Superficial, highly contagious zoophilic fungal skin disease of keratinized tissue
- Cats: Microsporum canis >> M. gypseum, M. persicolor, Trichophyton spp.
- Self-limiting, however treatment shortens course of disease and minimizes transmission to susceptible people or other animals
- Low-level zoonosis

Risk factors
- Juvenile (< 2 yrs) or geriatric cats
- Cats with poor body condition with concurrent or debilitating diseases
- Immunodeficient cats
- Physiological or social stress
- Immunosuppressive therapy
- Factors limited grooming – important defense mechanism (URI, obesity, arthritis)
- Factors that promote microtrauma - bites, scratches from other cats, ectoparasites, matted fur, macerated skin, poor hygiene and husbandry

Pathogenesis of infection
- Direct contact with infected animals most important for transmission to both cats and humans
- Exposure to infective spores in the environment or on fomites - lower risk of transmission
- Viable spores that contact skin surface need to defeat host protective mechanisms
- Spores begin adhering to skin within 2 hours
- Time from exposure to lesions = 2-4 weeks
- May shed spores BEFORE clinical signs!

Immunity
- Natural infection is rarely recurrent due to effective and long lasting immunity
- Cellular and humoral response is induced
- Th1 cells stimulate cell mediated response (IFN γ, IL-12 and 2) which results in recovery and protection against reinfection
- Role of humoral response unclear

Clinical signs
- Clinical signs and course of infection determined by pathogenesis of infection, cat’s immune response and overall health, and virulence factors

Clinical presentations
- Asymptomatic carrier
- Focal to multifocal alopecia - may be circular with scale and erythematous margin on head, distal limbs and tail with variable pruritus
  - Young cats have lesions that may start on bridge of nose, spread to temples and pinnae
- Miliary dermatitis (papulocrustous dermatitis) over dorsal trunk
- Diffuse alopecia /scale/inflammatory lesions
- Heavy crusts (similar to pemphigus foliaceus) with secondary bacterial infection and pruritus
- Paronychia (uncommon)
- Pseudomycetoma (Persian; rare) - marked inflammatory reaction to hyphae produces nodular granulomatous reaction involving dermis and draining to skin
  - Usually reported in Persian cats, but also in other breeds
  - Granulomatous panniculitis caused by M. canis with ulcerated nodules and yellow tissue grains
Clinical presentations relevant to treatment

- Simple infection – healthy cats or kittens with confirmed infection, obvious but limited lesions
  - Respond well to most therapy and may cure without medical intervention
- Complicated infection – widespread and/or inflammatory lesions, long-haired/matted coats, other illness (URI), older household cat exposed to new kitten, prior treatment for ringworm and/or feral cats
  - Do not cure until overall health is improved or normal
  - Lesion Free but Culture Positive – cats mechanically carrying spores on their hair coat or cats with very early lesions that are not easily seen contaminate environment and spread disease to other cats
  - Cats with true infection > 10 CFU/plate (often TNTC)
- Cats with fomite exposure < 5 CFU/plate - expect rapid change in culture status with topical therapy alone provided environment is clean
- Lesions? >> culture and treat as infected
- No-lesions? >> culture and recommend whole body treatment with antifungal rinse or shampoo

Differential diagnoses

- Patchy alopecia with scale: demodicosis, superficial pyoderma, drug eruptions
- Folliculitis/furunculosis: deep pyoderma
- Severe lesions with crust: auto-immune diseases (pemphigus foliaceus)
- Pseudomycetoma: deep mycoses, atypical bacterial infections, neoplasia

Diagnosis

- History and physical examination
- Wood’s lamp examination
- Microscopic examination of fluorescing hairs
- Cytology (if indicated to rule out other differentials)
- Deep skin scrapings for demodicosis
- Fungal culture
- Biopsy and histopathology – necessary for nodular form or atypical presentations
- Fungal identification requires culture or PCR

Wood’s lamp

- Valuable and under utilized screening tool
- UV light lamp of 360 nm wavelength
- Plug in model with magnification preferred (avoid battery operated models)
- Darken room and examine at distance of 4-10 cm
- Must take time to thoroughly examine hair coat
- Need to be trained to recognize positive hairs
- *M. canis* strains commonly fluoresce apple or blue green at shaft
- False positives: carriers (no active infection), medications, dust, carpet fibers, scale and crust
- Can find sites of infection that are not visible on gross clinical examination
- Valuable to select hairs for direct examination and culture
  - Positive hairs examined by direct examination confirm an infection
- Burton UV Wood’s light with magnification preferred

Microscopic examination of hairs (trichoscopy)

- Valuable in the rapid diagnosis of disease
- Pluck fluorescent hairs in the direction of growth from the periphery of the lesion
- Place hair on a slide with a drop of mineral oil +/- new methylene blue stain and cover slip
- Examine at 4x and 10x for “brush broken” pale, wide and filamentous hairs or hairs with an irregular surface; examine at 40x for arthrospores
- May use Wood’s lamp to identify fluorescence in mounted hairs
- May be positive in 60% or more of cases (depends strongly on the skills of the operator)
- False positives: internal root sheath and keratin of follicular casts
Fungal culture media

- Dermatophyte test media (DTM)
  - Contains phenol red as a pH indicator
  - Acids produced by catabolism of proteins turn media red
  - Inhibits saprophytic fungal growth
- Sabouraud’s dextrose agar
  - Contains gentamycin, cycloheximide and chlortetracycline to inhibit growth of bacteria and saprophytes
  - Allows better evaluation of colony color and macroconidia
- Sab-Duet (DTM/Mycobiotic plates) or Derm-Duet

Fungal culture technique

- Use sterile toothbrush and pluck fluorescent hair
- Brush ~ 20 times until visible hair is sampled sampling body and lesional areas last
- Distribute material evenly on the plate to allow maximum contact
- Inoculate circular plate from center and continue in centrifugal direction if concerned with residual topical therapy

Interpretation

- Label bottom of plate and place in sealed plastic bag
- Incubate at or above room temperature (~75-80°F) for 21 days with medium side UP
- Examine daily, record growth and CFU weekly - DTM turns red with mycelial growth in 4-7 days = POSITIVE
- Growth may be delayed in patient receiving treatment
- Pigmented fungi are not dermatophytes
- Some saprophytic fungi are positive for red color change; some dermatophytes are negative
- Must evaluate growth both grossly and microscopically

Microscopic identification

- Wear gloves and evaluate colonies at least 5 days old
- Press clear acetate tape on colony, then place a drop of lactophenol cotton or new methylene blue stain on a slide and allow to rest for 5-10 minutes
- Look carefully at 10x and 40x - some M. canis strains do not produce macroconidia; T. mentagrophytes macroconidia are difficult to find - look for spiral shaped hyphae

Pseudomycetoma - diagnosis

- Skin biopsy - place half in formalin; half in sterile saline for fungal culture +/- PCR
- Request special stains for fungi (PAS, Gomori silver stain)

Newer diagnostics

PCR

- Internal transcribed spacer of ribosomal DNA (ITS), is the genome fragment in most veterinary tests
- Ringworm RealPCR™ Panel offered by Idexx Laboratories includes Microsporum spp. and Trichophyton spp.
  - 95% sensitivity and 99% specificity (Idexx data on file)
  - Results in 1-3 business days
- Sensitivity may be problematic as carriers will test positive
- Need additional prospective studies

Dermoscopy

- Examination of skin using skin surface microscopy
- Used for evaluation for tinea capitus and pigmented skin lesions in humans
- Allows for visualization of infected hairs which appear “comma-like”
- In one study, dermoscopy identified three cats with infected hairs not yet detectable by Wood’s lamp
- In naturally occurring dermatophytosis, was positive in 21/36 with culture confirmed disease
- Useful in identification of hairs for direct examination and/or fungal culture

Management

- Reasonable confinement
- Environmental cleaning
- Topical and systemic antifungal therapy
- Monitoring until mycological cure

Management – Important points to emphasize

- Contracting dermatophytosis from casual contact with an infected environment is rare
- Dermatophyte spores are a dormant stage of the organism, do not live, grow or multiply in the environment
- Spores ≠ mold
- High humidity results in increased spore death
- Spores may survive in dry setting for 12 months, but majority are not viable and die within 3-6 months
- Spores are trapped by furnace filters and do not circulate via heating ducts
- Spores are easily removed from the environment

**Confinement**
- Facilitates cleaning and limits spread to other animals
- Needs to be appropriate for kittens that require socialization/family bonding and older cats that may need close monitoring; some cats will not eat well in absence of owner

**Cleaning**
- Removes infective material from environment and reduces false positive cultures
- Minimal impact on preventing infection of other animals and people
- If it can be washed, it can be decontaminated!

**Choosing a disinfectant**
- Instruct client to read entire product label and safety data sheet (SDS)
- Hard cleaning: gross removal of organic material and debris via sweeping or vacuuming followed by thorough washing with detergent until visibly clean
- One-step cleaners: clean lightly soiled surface + sanitize in one step; still need to remove organic debris!
  - Use between hard cleanings, not as a replacement

**Effective disinfectants**
- Sodium hypochlorite (bleach): 1:10 to 1:32
  - Short contact time but needs to be made fresh and used immediately
  - No detergent properties, may react with other agents and produce toxic gases, unpleasant odor, damage to surfaces, discoloration of fabrics, damage to floor finishes
- Enilconazole
  - Concentrated spray and fogger (Clindafarm®)
  - Not available in reasonably priced small volume
  - 10 minute contact time
- Accelerated Hydrogen Peroxide (AHP; Rescue® Virox Animal Health, others)
  - Becoming more available and very effective
  - Contains surfactants, wetting and chelating agents
  - 10 minute contact time
- Potassium peroxymonosulfate (Trifectant® Vetoquinol)
  - 10 minute contact time

**Effective OTC disinfectants**
- Choose product with label claim against *Trichophyton mentagrophytes*
- Active ingredients include: sodium hypochlorite, quaternary ammonium, lactic acid, AHP and ethoxylated alcohol mixture

**Decontamination recommendations**
- Hard, non-porous surfaces: perform 1-2x week
- (1) Remove debris - especially hair! (2) Wash with soap and water until visibly clean (3) Rinse well (4) Apply disinfectant (5) Remove debris and use one step cleaners and dusting between hard cleanings
- Wood floors, specialty counter tops – easily decontaminated by removal of debris and repeated washing
- Walls, windows, ledges – not necessary to hard clean unless large number of cats in environment; remove dust, etc. with Swiffer duster
- Soft surfaces, laundry - change blankets/bedding daily, store exposed laundry in plastic bag and separate from other items, use hot or cold water and bleach if desired (1 cup/tub), do not overfill – agitation is important, use longest wash
cycle and highest water level available, wash twice if large amount of hair is visible, wash pet laundry at end of day, mechanically clean laundry basin and lint trap, spray basin with disinfectant and run load with water only
- Dry cleaning - effective for decontamination, remove hair first, cleaner should handle as potentially contaminated and wear gloves when receiving items
- Carpets
- Difficult so best to limit contact with cat/kitten
- Steam cleaning may be effective - 95% of spores were removed 48 hours post cleaning
- If wash, need to thoroughly wet
- Vacuum to remove debris and hair, thoroughly spray with disinfectant, use carpet shampooer or deck brush to scrub, allow 10 min contact time, use carpet scrubber to wash carpet in the carpet with water until no foam remains
- May have massive sporulation on surface in 48 hrs - this is an exposure risk
- Bowls, litter boxes, pet carriers – wash twice using hot water, dish soap or a detergent and rinse well
- Dispose of cat trees unless fairly new with limited exposure and may be decontaminated, pet clothing, non-metal collars

Cultivating the environment
- Rarely indicated but consider in cases where lack of cure may be due to environmental contamination
- May help determine if cleaning is effective, however may be more effective to review cleaning protocol
- Collect two per room from floor and areas that cat frequents using Swiffer cloths and plate in house

Therapy
- No therapy? >> Spontaneous resolution in 70-100 days in healthy cats
- Why treat? >> Speed resolution of infection, avoid infection of other animals/humans, limit environmental contamination and false negative culture results
- Use combination of topical and systemic therapy

Topical treatment
- Why topical therapy?
- Only means of killing spores on hair coat
  - Limit spread of disease via direct contact
  - Minimize spore deposition in environment and the risk of false positive reactions
- Necessary and important part of treatment
- Lime sulphur and enilconazole are best options
- Comb prior to application of topical therapies - use flea comb and hand sanitizer

To clip or not to clip?
- Grossly reduces amount of infective material
- May require sedation, increase microtrauma and/or cause thermal burns that spreads infection
- Whole body clipping recommended if hair coat is matted, long hair with extensive lesions, soaking of hair coat is difficult, poor response to treatment
- Best to use scissors vs. clippers
- Infected whiskers may be clipped or plucked (if limited)

Topical treatment
- Whole body rinse with Lime sulphur (1:16), enilconazole (1:100), accelerated hydrogen peroxide (3.5% diluted 1:10) twice weekly
  - Apply lime sulphur and enilconazole to dry hair coat
- Dilute shampoo >/= 1:10 with 3 minute contact time - ketoconazole or miconazole 1-2% +/-chlorhexidine, climbazole 0.5%
- Climbazole 0.5% mousse
- Adjuvant focal therapy for areas difficult to bathe/rinse or remain positive - climbazole 0.5%, terbinafine 1% (human product), thiabendazole, clotrimazole, ketoconazole or miconazole at > 1%, vaginal miconazole may be used around the face/eye areas

Systemic therapy
- Why oral (systemic) therapy?
- Treatment of choice
- Only means of killing spores in hair follicle
- Dermatophytes may be cultured on non-lesional skin
- Shortens treatment time in combination with topical therapy
- Reduces environmental contamination in combination with topical therapy

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• Itraconazole 5 mg/kg PO once daily - available as tablet (100 mg), oral solution (10 mg/ml) and generic capsule (100 mg)
  o Treatment of choice - fungicidal
  o Inhibits the synthesis of ergosterol in the cell membrane
  o Concentrates in keratin and sebum, allows alternate day/alternate week treatment (one week on, one week off for six weeks)
  o Do not compound - impairs bioavailability and absorption
  o Side effects: increase in ALT correlates with toxicity, anorexia, vomiting, weight loss
  o Perform chemistry (ALT at minimum) once monthly during treatment

• Fluconazole: 5-10 mg/kg PO once daily - available as generic tablet (50, 100, 150 and 200 mg) and powder for oral suspension (10 and 40 mg/ml)
  o Fungistatic - mechanism of action similar to itraconazole
  o May need to reduce dose in cats with renal impairment
  o Side effects: inappetence, vomiting, diarrhea, hepatotoxicity (very rare)

• Terbinafine HCl: 30-40 mg/kg PO once daily - available as film coated oral granule (125 and 185 mg/packet) and generic tablet (250 mg)
  o Fungicidal - causes intracellular accumulation of squalene and inhibits ergosterol synthesis
  o Accumulates in high concentrations in sebum, stratum corneum and hair follicles and persists for 2-3 weeks after drug withdrawal
  o Alternate day/alternate week therapy as with itraconazole
  o Side effects: vomiting and intense facial pruritus reported

• Micronized griseofulvin – 25-50 mg/kg PO once-twice daily
  o Fungistatic - administer with fatty meal to increase absorption
  o Avoid in young (< 6 weeks) or immunosuppressed cats
  o Active in the stratum corneum for 36-72 hours
  o Requires long treatment periods - 5-6 weeks for hair/skin infection
  o Side effects - teratogenic - do not give within first 40 days of pregnancy, myelosuppression in FIV+ cats and selected breeds, and gastrointestinal signs
  o Perform CBC monthly

• -Safe and effective vaccine is not available for cats

Therapy - Monitoring
• Examination for presence or absence of lesions, examination with a Wood’s lamp, fungal culture with CFU count ALL important
• CURE = Clinical + Mycological Cure
• Number of CFU on a fungal culture plate reflects stage of infection and is important in monitoring
• Clinical cure precedes mycological cure
• Treat until at least two negative fungal cultures at 1-2 week intervals
• Persistently positive cultures + clinical cure + negative Wood’s lamp exam - need to evaluate environment

Normal skin but persistent positive culture?
• Fomite contamination (not true infection)
• Remaining subclinical lesion that have not healed
• Persistence of infective spores on distal portion of hair shaft
  o Most common in areas that are difficult to treat (face, ears)
  o Consider clipping fur with scissor or adjuvant topical therapy

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Cushing’s Disease in the Derm World

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Hypercortisolism is seen when there is an excessive amount of glucocorticoids present in the patient’s body. This increase in steroid levels can either be due to endogenous or exogenous glucocorticoid sources. A similar clinical appearance will be present in both sets of patients no matter the underlying cause of the increased cortisol levels. To make it even more difficult many times these patients present to the dermatology office with no evidence of PU/PD, panting, polyphagia, pot belly and/or liver enzyme elevations to support the diagnosis. Some clinicians believe that unless these systemic signs are present, a diagnosis of hyperadrenocorticism is very unlikely and thus a patient should not be treated. However, many times cutaneous signs can precede systemic signs and one should always screen for this disease if the clinical suspicion is high.

Iatrogenic hyperadrenocorticism

In veterinary dermatology, oral, injectable and topical steroid use is rampant, so sometimes it may be difficult to determine if a particular patient could have natural or iatrogenic cushings. It is very important to get a very accurate medication history from these patients. Clients many times will forget about topical medication administration which can sometimes contain very potent topical steroids. The author has seen two cases where the owners were using so much of a topical steroid powder that they both developed iatrogenic cutaneous lesions and were misdiagnosed as having addisons disease after both patients experienced gastrointestinal distress due to a completely unrelated issue.

In order to test for iatrogenic cutaneous lesions the recommended protocol requires the collection of a pre-ACTH serum sample, prior to administration of 5 µg/kg of synthetic cosyntrophin, IV. A post-serum sample is then collected 1 hour later. A dog with iatrogenic HAC should have a flat-line response, generally with both baseline and 1 h post-stimulation values of < 1 µg/dL. It is important to note that even short courses of glucocorticoids may inhibit the adrenal response to ACTH for up to a month or more.

Calcinosis cutis

Calcinosis cutis is an uncommon occurrence, in which inorganic, insoluble mineral salts are deposited in the dermis, subcutis or, rarely, the epidermis. When related to excess steroids it is considered dystrophic mineralization. Lesions are firm white-pink to yellow firm dermal papules to plaques. Overtime as this calcium remains in the skin the area will start to become ulcerated and create large crusts which can become very pruritic. These changes tend to occur on the dorsal neck, rump and axillary and inguinal regions. These areas can get frequently infected with both bacteria and yeast which can lead to pain. Anytime these changes are seen clinically, or via a biopsy, this patient must be screened for Cushing’s disease and ensure no exogenous steroids are being given. One must remember that this disease will get better before it gets worse. One must also warn the clients that the calcium deposits will continue to appear for some time after diagnosis and treatment for hyperadrenocorticism is started. Controlling the cortisol levels will be the best long term treatment but DMSO has been shown to help resolve the lesions as well. DMSO is generally applied daily to twice daily to the lesions but can have a very strong odor for some clients. I also always warn by owners to wear gloves when applying given the medications ability to help with topical drug absorption. It is recommended with more extended use that serum calcium levels should be monitored to ensure that excess calcium is not entering the blood stream. However, the author has never seen this occur clinically.

Depending on the extent of the calcium deposits sometimes patients will have clinical lesions for years and years and some owners elect to surgically remove the more problematic areas.

Adult onset demodex

Any patient that presents with skin lesions that first develop at a middle to older age should always be skin scraped to ensure demodecites are not present. In one retrospective study 20% of patients diagnosed with adult onset demodicosis were later diagnosed with hyperadrenocorticism as the underlying disease.

Clinical lesions are similar to those seen in juvenile onset demodicosis. Lesions include erythema, comedones, scaling progressing to partial to complete alopecia with papules, pustules, and hyperpigmentation. Severe cases may be associated with lymphadenopathy, lethargy and fever as well as furunculosis with scales, crusts, exudation and focal ulceration and draining tracts. Pedal demodicosis may be associated with significant interdigital edema and, particularly in larger dogs, may be painful. A secondary bacterial skin infection almost invariably accompanies generalized demodicosis and may lead to pruritus.

Diagnosis will be by multiple skin scrapings, trichograms, and/or biopsy.

Treatment will involve management of secondary infections, control of primary hyperadrenocorticism and appropriate acaricidal medications. Once the cortisol levels have been lowered patients may be able to be cured and not relapse with disease unless cortisol levels raise again.
**Dermatophytosis**

Dermatophytes are transmitted by contact with infected hair or fungal elements on other animals, on fomites or in the environment. Canines are usually infected with *M. canis* (transmitted from an infected cat), *Trichophyton* spp. (exposure to infected rodents), or *M. gypseum* (from the soil)\(^6\). Typical lesions are collarettes, scales, crusts and/or papules. This is a disease of patients less than one year of age so when present in the mature patient one must determine if there is an underlying condition that is present causing immunosuppression\(^1\).

**Adult onset bacterial and yeast infections**

This is perhaps the most common reason I screen patients for hyperadrenocorticism. As we know it is not common for a patient, with no previous history of skin disease, to suddenly start presenting with multiple geriatric onset bacterial and yeast skin and ear infections. These adult onset infections can sometimes be very severe and yet some are relatively non-pruritic\(^4\).

These patients many times will do very well while they are on antibiotics and/or anti-yeast medications and then the infection will return shortly after finishing the treatment course. Patients are screened for cushings disease based on their re-occurrence rate. I generally will not screen patients if the infection resolves quickly and without incident. However, if the infection and pruritus returns in less than 3-4 months I will recommend a low dose dexamethasone suppression test or ACTH test to be performed.

Unless the cortisol levels are managed these infections will continue to occur. This patient will often need extended coarse of antibiotics rather than the standard 4 weeks since they are immunocompromised until the cortisol levels drop to a normal range.

**Hypersensitivity dermatitis**

These cases can be the most frustrating for the clinician and the client and there are two main presentations.

One presentation is where patients present at a younger age with pruritic skin disease and then are spot treated, or even placed on long term allergy medications. As this patient ages, gradually their allergies seem to significantly improve through time. Many times owners describe to me that they feel that their animal “has grown out of their allergies”. Then slowly these animals start to have re-occurrence of their secondary infections and pruritus. These patients were essentially self-medicating their allergies with their endogenous production of cortisol. To the owner they feel that the allergies are back when in actuality it is another clinical disease.

The other common presentation is patient that have a long history of mild skin disease and suddenly patients start to get worse and worse clinical lesions as they age. Once their infections are treated they do better for a period of time and then the cycle restarts. These patients will generally have lesions first and then develop pruritus after the rash is present.

Despite the historical presentation both of these patients may slowly start having their pruritus (from their allergies) return once their cortisol levels have dropped to a more normal range. Some clients will see no real clinical change in their patient’s comfort despite medical treatment. Their pet may still get itchy and secondary infections but now it is due to their uncontrolled allergies rather than the hyperadrenocorticism. Educating owners from the start about what to expect is key especially if you know a patient has a history of allergic skin disease. That way they understand that sometimes multiple medications may be needed to keep a patient’s cortisol and allergies at a tolerable level. There have been many times when the author has needed to use more potent allergy medications once treatment for cushings has started. This may also play a role in how low you want their cortisol levels while on therapy. Some clinicians have been known to use lower doses of trilostane and/or mitotane to gather clinical benefit for allergies and sometimes osteoarthritis.

**Coat changes**

Some of the first signs that astute owners will notice is that gradually the coat loses its luster and becomes a coarser texture. Clients that own dogs with long hair growth cycles (poodle) may also increase the time in between grooming appointments because the hair is no longer growing as fast. This will eventually lead to hypotrichosis and then complete alopecia. The hair on the head and the distal extremities tends to be spared whereas the trunk and tail experience a majority of the changes. However, non-truncal patchy alopecia can occur in up to 13% of patients with HAC\(^8\).

Along with changes in the quality and the quantity of hair the color itself can change as well. Black hairs turn auburn or light brown colored and brown hairs lighten to tan or blonde. This change in pigmentation can occur along the entire length of the hair shaft or only at the distal aspect. In the cases where only the distal tip is affected patients can appear sun bleached.

**Skin changes**

Other cutaneous signs include: thin skin that can wrinkle very easily, generalized and/or localized hyperpigmentation, with atrophied sebaceous glands and hair follicles. These patients will also easily bruise and create petechiae, ecchymosis and even phlebitis. Comedones, milia and poor wound healing are also important cutaneous changes that occur in the patient with hyperadrenocorticism\(^1\).
Pruritus
This is perhaps the most unexpected findings in dogs with cushings disease. However, several studies have seen a small number of cases where pruritus (pedal and limb pruritus) was present at the time of diagnosis and resolved once treatment with mitotane was started1. It is thought that the pruritus may be associated with neurosis as noted in people with cushings disease.

Treatment and conclusion
Hyperadrenocorticism is a clinical disease that warrants treatment many times in the dermatological setting. Anytime a patient is diagnosed with recurrent adult onset infectious diseases (parasitic/bacterial/fungal) or calcino
cutis one must screen for the presence of HAC. Once confirmed the cortisol levels must be lowered for those patients to lead a more comfortable life long term. Most patient’s cutaneous signs (resolution of infectious diseases, alopecia, coat changes) will resolve within about 3 months of treatment initiation but calcinosis cutis may take many years, if ever, to resolve.

References
Demodex canis is a non-contagious parasitic skin disease seen in dogs. This disease is usually divided into localized and generalized disease. In young animals, endoparasiticism, malnutrition, estrus, and debilitation may lead to an immunocompromised state that favors mite proliferation and development of skin disease. In adult animals with demodicosis, disorders such as hypothyroidism, hypercortisolism [naturally occurring or iatrogenic], leishmaniasis, malignant neoplasia [especially indolent lymphoma], and immunosuppressive treatments for cancer or autoimmune diseases have been recognized. In more than 50% of cases no underlying cause was found for the adult onset demodex. However, if initial screening tests (X-rays, thyroid panels, ACTH tests, and abdominal ultrasounds) were normal patients should still be monitored carefully because the primary illness causing the demodicosis may become evident months later.

In many publications, a juvenile-onset and an adult-onset form of the disease are differentiated. However, this differentiation may be difficult in individual cases. It is more important to identify and correct predisposing factors or underlying diseases independent of age, to achieve the best possible outcome.

Localized onset demodicosis occurs where there are only a few (generally less than six) areas of alopecia and scaling in a patient where mites are discovered on skin scraping. These patients generally do not require treatment and will spontaneously resolve.

Generalized demodicosis: Exact definition varies but generally a patient is considered to have generalized demodicosis when that patient has many localized lesions, involvement of an entire body region or has complete involvement of two feet or more. May be severe and a potentially life-threatening disease. Lesions include erythema, comedones, scaling progressing to partial to complete alopecia with papules, pustules, and hyperpigmentation. Severe cases may be associated with lymphadenopathy, lethargy and fever. Generalized demodicosis is thought to be a hereditary based disease. In addition, there appears to be a Demodex specific T-cell defect that does play a role in severity and this defect is thought to be hereditary.

Diagnosis

Very easily done with simple multiple skin scraping, trichograms or via biopsy.

There are four stages of Demodex canis mites that can be seen on tape cytology and skin scrapings. These stages include fusiform eggs that hatch into six-legged larvae, which mature into eight-legged nymphs and progress to eight-legged adults. If one were to scrape a normal puppy numerous times in areas around the mouth and paws you will probably see a mite or two, however the puppy will not have any clinical lesions.
The skin scrapings have the best yield when primary lesions [e.g. follicular papules, pustules] chosen and skin is squeezed. If one mite is found, additional skin scrapings should be performed. Finding more than one mite is strongly suggestive of clinical demodicosis.

Trichograms are useful in areas that are difficult to scrape, such as periocular and interdigital areas. Negative trichograms should be followed by deep skin scrapings before ruling out demodicosis.¹

Skin biopsies may be indicated in Shar-Pei dogs or from very fibrotic lesions (especially interdigital).¹

There has been no study that has validated the prognostic value of percentages of immature forms or alive parasites on samples so I look to see if the mites are dead or alive and how many total present as my way of evaluating treatment.

Therapy

Localized demodicosis does not require treatment but I highly recommend periodic follow-ups to ensure that the disease is self-resolving and that the patient is not progressing into the generalized form.

For many years, veterinarians relied on a short list of medications for the treatment of generalized demodex however this has recently changed.

Amitraz: Traditionally, patients had been treated with dips at concentrations from 0.025% to 0.05% once a week to every other week. It is effective in 50 to 86% of patients and the higher concentration and more frequent dips were probably associated with a higher success rate. Amitraz can be toxic and the use of gloves and one will need a well-ventilated room to perform the treatment¹

There was a spot-on which included Amitraz that was fairly effective at treating demodex however this medication is currently not being manufactured and was associated with the development of localized and generalized pemphigus⁹,¹⁰

Macrocyclic lactones (avermectins and milbemycins) are a very common choice for the treatment of demodex.

Ivermectin is an avermectin with a gamma-aminobutyric acid (GABA) agonist activity. Ivermectin is given daily at 0.3 to 0.6 mg/kg until three negative scrapings at one month intervals are obtained. The bovine injectable form of the drug is administered orally as a solution. Ivermectin should not be used in Collies, Shetland sheepdogs, Old English sheepdogs, Australian sheepdogs, and their crosses due to the mutation in ABCB1 (formerly MDR-1) gene. Signs of toxicosis include mydriasis, ataxia, weakness, recumbency, coma and even lead to death¹

Milbemycin (interceptor⁶) is a natural fermentation product produced by Streptomyces hygroscopicus aureolacrimosus. It is closely related to the avermectins, produced by Streptomyces avermitilis, differing only in one position. The anthelminthic activity is believed to result from disruption of invertebrate gamma amino butyric acid (GABA) neurotransmission. Daily doses of 0.5 up to 3.1 mg/kg per day have been shown to have a 60 to 96% cure rate in a few months (up to about 1 year)⁸

Moxidectin is derived from fermentation products of Streptomyces cyaneagrisus subsp. Noncyanogenus. Oral formulation has been used at 0.4mg/kg daily and shown to be effective.¹¹ There is also a spot application formulation available for dogs which has 2.5% Moxidectin and 10% imidiclopramide. The product is licensed for application every 4 weeks, but more frequent application (weekly to every other week) is often needed when treating Demodex¹²

Isoxazoline: Are a novel class of parasiticides that are potent inhibitors of GABA-gated chloride channels and glutamate-gated chloride channels.

Afoxolaner: (NexGard⁸): Afoxolaner was administered to eight dogs at the recommended dose (at least 2.5 mg/kg) on Days 0, 14, 28 and 56. The topical combination of imidacloprid/moxidectin was given at the same intervals at the recommended concentration to eight patients as well. Clinical examinations and deep skin scrapings were performed monthly. The percentage reductions of mite counts were 99.2%, 99.9% and 100% on Days 28, 56 and 84, respectively, in the afoxolaner-treated group, compared to 89.8%, 85.2% and 86.6% on Days 28, 56 and 84 in the imidacloprid/moxidectin-treated group¹³

Fluralaner: (Bravecto™) Sixteen dogs, all diagnosed with generalized demodicetic mange, were randomly allocated to two equal groups. Bravecto™ chewable tablets were administered once orally at a minimum dose of 25 mg fluralaner/kg body weight to one group of dogs, while the second group was treated topically on three occasions at 28-day intervals with Advocate®. Mites were counted in skin scrapings before treatment and at 28-day intervals over a 12-week study period. A single oral administration of Bravecto™ chewable tablets, mite numbers in skin scrapings were reduced by 99.8% on Day 28 and by 100% on Days 56 and 84. Mite numbers in the dogs treated topically on three occasions at 28-day intervals with Advocate® were reduced by 98.0% on Day 28, by 96.5% on Day 56 and by 94.7% on Day 84¹⁴

Sarolaner: (Simparica™) Sixteen dogs with generalized demodicosis were randomly assigned to treatment with either sarolaner orally on Days 0, 30 and 60, or topical imidacloprid (10 mg/kg) plus moxidectin (2.5 mg/kg) solution every 7 days from Day 0 to Day 81. For sarolaner-treated dogs, pretreatment mite counts were reduced by 97.1% at 14 days and 99.8% by 29 days after the first dose. Weekly imidacloprid plus moxidectin resulted in 84.4 and 95.6% reduction at these two time points¹⁵

Infection control: Generally patients with generalized demodex will also have superficial and/or deep infections. Appropriate systemic antibiotics and antifungals may be necessary for minimum 4 weeks treatment duration. Topical antimicrobial based shampoos should also be implemented to decrease treatment interval.
Glucocorticoids are absolutely contra-indicated, even topically (cutaneous or auricular topicals) even if pruritus is severe.1

Monitoring and prognosis
It is not sufficient to rely on clinical appearance as the end-point of treatment. Clinically normal dogs may still harbor mites on deep skin scrapings. Microscopic cure, defined as multiple negative skin scrapings, in addition to resolution of clinical signs is needed to determine the therapeutic end-point. In general, it is recommended to scrape the three to five most severely affected areas and any new lesions monthly until all scrapings are negative. It is recommended to continue treatment for 1 month after the second negative monthly set of skin scrapings.1

The prognosis for canine demodicosis is good, with the majority of cases achieving long-term remission.8 However, dogs with an incurable or poorly controlled underlying disease may never be cured and may require long-term therapy with the newer generation flea preventatives this is an easier situation than it was even 3 years ago. The current recommendation is to avoid long-term glucocorticoid therapy in dogs with a history of demodicosis.1

Demodex inaj
In 1997, Dr Andrew Hillier presented at the AAVD/ACVD annual meeting in Nashville a canine skin disease due to a novel Demodex mite. This mite has a much longer body than Demodex canis and in 2003 it was coined demodex inaj.

Clinical features
Can cause a greasy seborrhea mainly on the dorso-lumbar and facial area. Breeds that are predisposed include the West Highland White, Shih Tzu, and Scottish terrier. Mites counts tend to be very low so alopecia may not be evident but patients can sometimes be very pruritic. Excessive glucocorticoid therapy (for allergy and pruritus) and hypothyroidism have been reported as underlying causes.3

Diagnosis
Skin scrapings, trichograms, and a biopsy may be needed in some cases due to scarcity of mites.

Therapy
See above

Demodex cornei
A short-bodied Demodex mite that may exclusively live in the stratum corneum. It could be a mutant of D. canis or a new species. So far the mite is present in cases of simultaneous infestation with Demodex canis. Therapy is the same as for D. canis.2

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Fleas, Fleas, and More Fleas
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There are more than 2,000 species and subspecies of fleas and dogs and cats can be the transient host for any of these species. However, *Ctenocephalides felis felis*, *Ctenocephalides canis*, *Pulex spp.*, and *Echidnophaga gallinacea* are the one ones of medical concern. Overall *Ctenocephalides felis* is the one of most concern in the United States and Worldwide.

Flea life cycle
The flea depend on the host for food and protection so they will spend the almost entire adult life of the animal. The female flea will lay her eggs on the host usually while the animal rests or sleeps. These eggs quickly fall off the host and contaminant the environment. Flea eggs usually hatch in 36 hours and some make take up to 10 days. Low temperatures (<0°C) for 24 to 36 hours are lethal to most eggs. The eggs then hatch into larva which move to the dark protected areas like deep into carpets due to their negative phototaxis and positive geotropism. Larva are the most sensitive stage in the flea life cycle and only about 25% will survive in the environment due to lack of food, dryness, and extreme temperatures. The third instar of the larva will then form of a cocoon and form a pupa. The pupa is more hardy than all the other stages but will die at the extreme temperatures. The adult flea can remain in the cocoon for as long as 140 days before emerging with proper temperature and humidity. In most households, C. felis will take 3 to 4 weeks to complete its life cycle so it is very important for flea infested households to understand that despite starting flea control they may still see fleas that first month or two.

The newly emerged adults require a host for long-term survival. Once on a host, c felis initiates feeding within seconds to minutes. Feeding is so rapid that partially digested blood can be defecated in as little as 2-6 minutes after fleas acquire a host. Mating occurs on the host after feeding and the female c felis begin egg production within 24-36 hours after their first blood meal. With peak egg production a single female flea can lay between 40-50 eggs per day.

Flea control
Flea are essentially everywhere and depending on the area can either be a seasonal or year round issue for pet owners. All animals are considered at risk and those that frequent grooming facilities, doggie day care, dog parks, have or access to wildlife populations are at even higher risk. Effective treatments used on the animal can eventually eliminate environmental fleas, provided that untreated animals do not reinfect the area.

External environment
Because flea eggs fall to the ground, the infested pet’s yard can be seeded with fleas by the pet itself or by stray dogs, cats, opossums and raccoons. As discussed earlier flea larva are very sensitive to heat and desiccation and given this fact, adults should not develop on paved areas, on deck surfaces, or in short-cut, un-exposed lawn. The areas that are protected from the direct sun and have some form of shelter are the largest problem areas. This would include area under decks, overgrown brush, and crawl spaces. These are the areas to be concerned about when treating the environment. There are many different products out there that can treat the environment including carbamates or organophosphates that are available in liquid and powders. For those families wishing to have a more natural approach there is a company marketing beneficial nematodes (Fleabusters). This product contains harmless nematodes called Steinernema carpocapsae, which kill flea larvae and pupae in the grass and soil. The efficacy of this system is not known.

Internal environment
This is usually the hardest part of flea control and prevention and requires thorough cleaning. Vacuuming will help remove eggs, larva and adults but may also cause adults to emerge. Once must remember to empty the bag or canister after each process. Dog beds and carpets should be washed or replaced.

Hiring a profession may be the best recommendation since they have access to many products that we do not and they are familiar with the proper application. However, many products are available to treat the interior of a house. For the client that has significant issues with the use of these products sodium borate would probably be the best recommendation. The borate compounds have rapid ovicidal and larvicidal activity, which is suspected to be through a dehydrating mechanism. The professionally applied product (Rx for Fleas, Inc.) is guaranteed for 1 year, provided carpets are not cleaned, and has a reported efficacy of greater than 99.5.

For prevention of re-infestation another good option would be the use of insect growth regulators. These products prevent the larva from transitioning to the pupa stage. If these products are applied in the house before fleas are introduced, infestation should be aborted. Methoprene is degraded by sunlight and should be reapplied at least every 30 weeks. Fenoxycarb and pyriproxyfen are sunlight stable and last 6 to 12 months.
For use on animals
The following is a table of the most commonly used products that are administered to the patient themselves.3,8,9

<table>
<thead>
<tr>
<th>Key Drug</th>
<th>Drug Class</th>
<th>MoA</th>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinosad</td>
<td>Macrocyclic lactone</td>
<td>nAChR agonist</td>
<td>Contraindicated with high dose ivermectin GI upset somewhat common</td>
</tr>
<tr>
<td>Afoxolaner</td>
<td>Isoxazoline</td>
<td>GABA and Glutamate antagonists</td>
<td>Effective against demodex and some tick species Highly palatable Minimal upset stomach Fluralaner = effective for 12 weeks</td>
</tr>
<tr>
<td>Fluralaner</td>
<td>Sarolaner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selamectin</td>
<td>Avermectin</td>
<td>GABA agonist</td>
<td>Fleas continue to feed during first hour. Peak efficacy not seen for 36-42 hours Effective against sarcoptic mange when applied q 2 weeks x 3 applications</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>Neonicotinoid</td>
<td>nAChR agonist</td>
<td>Efficacy within 6-12 hours Fleas stop feeding within 3-5 minutes</td>
</tr>
<tr>
<td>Fipronil</td>
<td>Phenylprazole</td>
<td>Insect GABA receptor agonist</td>
<td>Fleas continue to feed during first hour. Toxic to rabbits</td>
</tr>
<tr>
<td>Dinotefuran</td>
<td>Neonicatinoid</td>
<td>nAChR agonist</td>
<td>Vectra 3D product contains permethrin, do not use in cats</td>
</tr>
<tr>
<td>Pyriproxyfen</td>
<td>Insect growth regulator</td>
<td>Juvenile hormone analog</td>
<td>Mode of action similar to methoprene but not UV sensitive like methoprene</td>
</tr>
<tr>
<td>Permethrin</td>
<td>Pyrethroid</td>
<td>Target voltage gated Na+ and Ca+ channels</td>
<td>Kills ticks, biting flies, and mosquitoes Toxic to cats Repellent action Most EPA reports of &quot;major pesticide reactions&quot; involved spot-ons containing pyrethrins</td>
</tr>
<tr>
<td>Nitenpyram</td>
<td>Neonicatinoid</td>
<td>nAChR agonist</td>
<td>Onset within 30 minutes 100% efficacy within 4-6 hours Little residual activity within 48 hours</td>
</tr>
</tbody>
</table>

Therapeutic plan for the flea infested pet
When encountering a patient for the first time with either clinical signs related to flea allergy dermatitis or who is flea infested one must take an accurate history. Determine if that patient frequents areas where fleas could be commonly found (dog parks etc) and also discuss the outdoor environment at home. Question the owner about the possibility of wildlife in the area and if there is a lot shaded areas the patient likes to frequent. Then start prescription flea preventative for all pets in the household. Treat the pruritus and any secondary pyoderma with appropriate medications. Make sure you pick a preventative that fits with the client's preferences (oral vs. topical) any concurrent dz (food allergy, flea allergy, demodex mites), the pet's lifestyle (tick exposure, bathing frequency)

Advice for clients
Clients many times will say their flea control doesn't work. These clients will need to be educated about the flea lifecycle and feeding behavior. Advise them that while our prescription flea preventative are highly effective, they take time to kill fleas and do not prevent all feeding3. Fleas will need to bite the pet before being killed by the adulticide. It is likely that owners will see live adult...
fleas on their pet after having given a flea preventative, but it is highly unlikely they will have an infestation when prescription flea prevention is used on a consistent monthly basis. Remind them that flea preventatives do not create an invisible force field that kills every flea before it jumps onto the pet.

**Clients who do not believe fleas are the problem**

You do not have to see the flea for the flea to cause a reaction. Use a peanut allergy analogy to help them understand: If a person is allergic to peanuts, one peanut may touch their food and they will have a reaction. They do not have to see the peanut. Repeat the history they gave back to them, wait for them to validate that you have the story straight. Then, present the fact that itching and secondary infections in the back half of the body is textbook for flea allergy. Explain that every flea medication, just like every drug of any kind, wanes in efficacy from the time it is given to the time the next dose is due. A pet on good monthly flea control will never have an infestation, because fleas that infest the pet will die before they have enough time to lay eggs. However, for a pet that is sensitive, a few hours of feeding before the flea dies may be enough to cause a reaction. For this reason, hypersensitive pets do better on bi-monthly flea prevention. Compliment the owner on the cleanliness of their home and their pet, advise them you are sure their pet would never have an infestation. However, remind them that with all the good work they are doing and money they are spending on allergy work-up it would be a shame for a future flea bite to confound analysis of the itch level and potentially lead us astray in our diagnosis.

**Clients who are concerned about safety**

Flea preventatives exploit a difference in the nervous system between insects and mammals. It is anatomically/physiologically impossible for these products to kill a mammal the same way they kill fleas. Adverse reactions may occur as they can with any oral or topical product of any kind, but the benefits far outweigh the risks. Point out that monthly or bi-monthly flea prevention is a lot safer than repeated courses of steroids and antibiotics to manage the symptoms. Explain that the majority of reported adverse reactions in pets and people are involve topical products containing pyrethrins or older organophosphates and carbamates. These products may or may not have been used appropriately by the owners (e.g. pyrethrins may have been applied to cats). Explain that some topical products such as imidacloprid are not systematically absorbed. While dermal hypersensitivity reactions can occur, point out that this is also true with any soap or lotion we would use on ourselves. Many dermal reactions are related to carrier ingredients rather than the insecticide. Inform clients of the diseases which can be caused and/or transmitted by fleas. These include iron deficiency anemia, rickettsia typhi, rickettsia felis, bartonella henselae, mycoplasma haemofelis, yersinia pestis, dipylidium caninum. Educate them that these diseases are worse than flea infestation and may require treatment that is less safe than prescription flea preventatives. Use of the broader term "parasites" can sometimes invoke greater willingness of the owner.

**What about 'natural' flea preventatives?**

These medications are typically ineffective, this is usually easy especially once you educate them and potentially point out evidence of fleas on their animal. Also 'natural' does not always mean safe, garlic can cause anemia and Tea Tree oil (melaleuca) can cause transient hind-limb paresis, hepatotoxicity and is commonly implicated in atopic disease. Other ingredients like peppermint, clove, cinnamon, lemongrass and thyme have been links with dermal reactions are related to carrier ingredients rather than the insecticide. Inform clients of the diseases which can be caused and/or transmitted by fleas. These include iron deficiency anemia, rickettsia typhi, rickettsia felis, bartonella henselae, mycoplasma haemofelis, yersinia pestis, dipylidium caninum. Educate them that these diseases are worse than flea infestation and may require treatment that is less safe than prescription flea preventatives. Use of the broader term "parasites" can sometimes invoke greater willingness of the owner.

**References**

Pruritus in puppies may be one of the most difficult diseases that can present in clinical practice. This is due to many factors including: client frustration, the relative lack of safe treatment recommendations to decrease pruritus, constant changing weight of the patient, and the fact that sometimes a clear diagnosis is not available/obtainable.

Client education
Many times owners are already very irritated by the time they make an appointment to be seen. The puppy they just adopted is showing signs of illness and this is not what they expected to be managing at such a young age. In addition, training and housebreaking is a much more challenging experience if the drive to itch is so intense that the puppy cannot focus on the task at hand which can frustrate the client even further. Empathizing with the client’s situation and explaining all the different possibilities/treatments that are available is a must.

History
Just because the patients are so young does not mean that your history should be limited. Knowing if the patient came from the shelter and/or a breeder and if any of the littermates are affected can be a valuable pieces of information that can help narrow down the possible differentials. The client should also be questioned about travel history prior and post adoption. In the particular area that I work I have seen numerous dogs flown in as young adults/puppies from Africa, South American, Mexico, Middle east and all through-out the United States. There is some dermatological disease that will be more common in foreign counties than in the US so this may change your differentials.

In addition, I always ask what type of life style does this patient have? With the growing trend of doggie day care, hiking/walking groups, and dog parks canines have much more of a social lifestyle than ever before. This type of interaction can lead to increased flea exposure and other contagious diseases and can give you information about any other animals affected within the same social group.

The client should always be questioned regarding the main areas of the body that the puppy is itching/licking, how severe the pruritus is, and response to any previous medications that have been given.

Physical examination
Many of the pruritic puppies I have seen have completely normal physical examinations. However, one must always perform a pinnal-pedal reflex in young patients on their first examination. The reflex is assessed by rubbing the tip of an earflap on to the base of the ear for several seconds. This test is considered positive if the ipsilateral hind leg makes a scratching movement. This test has been shown to have a sensitivity of 81.8% and a specificity of 93.8% of dogs in a study of 588 patients. Along with the testing of the pinnal-pedal reflex the patient should be flea combed and one should ensure there is no evidence of flea dirt as well.

Diagnostics
1. Superficial skin scrapings should always be performed in all itchy young patients. For the superficial scrapings I will often scrape the pinna and the lateral elbows and hocks and the examine the specimen at 10x. If I am very suspicious of scabies, I will often take numerous scrapings (sometimes more than 5) to see if any mites/eggs/fecal pellets are found.
2. A deep skin scraping is also performed generally at the face, at least one of the paws, and then 1 or 2 other clinically affected areas. The material is placed on separate slides and viewed at 10X to help determine if demodex mites are present and if present is the disease localized or generalized.
3. Surface cytology: Any papules, pustules, crusts or areas of lichenification are sampled and examined at 100x for any signs of bacteria and/or yeast organisms and to evaluate the inflammatory cells present.
4. Fungal culture: Although generally not considered an itchy disease one must consider performing a fungal culture on young puppies that present with lesions consistent with a folliculitis and/or hair loss. I have personally seen extremely itchy dogs that had a primary dermatophyte infection and their pruritus resolved once the dermatophyte was cleared this is mainly seen with Trichophyton and M. persicolor infections in dogs.

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Diseases

**Sarcoptic mange**

Intensely pruritic, contagious disease caused by Sarcoptes scabiei var. canis. This is considered a zoonotic disease and clients should be warned about the potential for transient lesions. In canine mites prefer the skin of the ears, elbows, abdomen and hocks where there tends to be less hair. Patients obtained recently from the shelter and animals that attend dog parks and doggie day care are at increased risk. Patients tend to be mostly itchy at the ears and face and the entire ventral surface with the dorsum essentially spared.

**Clinical lesions**

Intense pruritus will be the main clinical sign and these dogs will sometimes have to be manually restrained in the exam room. The initial lesions are generally crusted papules that can progress rapidly to alopecia, erythema, and thick yellow crusts. Some patients do not show any lesions at all beyond pruritus. The level of pruritus is directly related to the number of mites present. The pruritus seen is from a hypersensitivity reaction to the mites themselves.

**Diagnosis**

Can be very difficult to diagnosis since even after numerous scrapings; anywhere between 20-50% of the time the mites, eggs and/or fecal pellets are not found. Many clinicians rely on response to adequate medications as their main way of diagnosing this disease. As we discussed earlier, a positive pinnal-pedal reflex is helpful for screening for potential cases. Fecal flotation can also sometimes find mites due to excessive grooming behavior is affected animals. An ELISA test exists for the diagnosis of scabies and is between 84- 92% sensitive and 90- 96% specific. However, it can take up to 5 weeks for an animal to start producing adequate antibodies to illicit a positive test.

**Treatment**

At this time there are many ways to treat this disease and choice of medication will depend on patients age and owner’s preference. If patient lives in a multi-dog household all animals must be treated for resolution. 2-4% lime sulfur dip weekly for a period of 4-6 weeks has proven to be effective and does have additional anti-pruritus properties for the patient. Ivermectin at weekly administration between 0.2-0.4mg/kg has also been used at every two week intervals for three injections or orally once weekly for 6 weeks. Other effective medications include selamectin, imidacloprid/Permethrin, and milbemycin, and several of the new generation isoxazoline flea medications like sarolaner.

**Pelodera strongyloides**

Small nematodes that lives in decaying material in the soil where it normally completes its entire life cycle. However, the third stage larvae are capable of penetrating human and mammalian skin and can cause a severely pruritic dermatitis. Generally, these animals live in the Midwestern United States and have access to damp straw bedding.

**Clinical lesions**

Creates a pruritic dermatitis that will occur on parts of the body in contact with the damp bedding. Commonly lesions will be on the ventral abdomen, chest, perineum, legs, lateral shoulder and thighs and spares the head and back. This nematode can cause alopecia, erythema and crusted lesions in sites infected.

**Diagnosis**

You can find these nematodes in skin scrapings and are generally between 600-750 µm in length and 30-40 µm in width. The clinician should ensure that the nematodes found are not a type of hookworm. One can also diagnosis this disease via biopsy where the larva are found inside hair follicles.

**Treatment**

Complete removal of the contaminated bedding is mandatory to reliably treat these animals. All areas must be washed and sprayed with insecticide. To treat the patient one can use Ivermectin but once the environmental is cleaned patients can undergo spontaneously resolution.

**Ancylostoma and uncinaria**

Larva are present on grasses and soils during the spring and summer season. They are seen patients that live in large capacity dog kennels and in patients that frequent dog parks that are not properly maintained.

**Clinical lesions**

Red papules on the skin that come in contact with the soil/grasses. As the disease progresses these areas become thickened and alopecic. The paws can become erythematous and may become swollen and pruritus is variable but always present.

**Diagnosis**

Positive fecal examination for hookworms and compatible clinical signs can usually lead to a diagnosis. However, if the fecal examination is negative one can perform a biopsy to aid in the diagnosis. Histopathology can reveal a perivascular dermatitis and recent larval migrations tracts can sometimes be seen. Larva are not usually present on biopsy samples

**Treatment and prevention**

The widespread use of heartworm preventives that also have anti-helminth activity has minimized this disease. Treatment should emphasize cleaning of the premises, frequent removal of feces. Once can use pyrantel pamoate tablets or fenbendazole for treatment but keep in mind the treatment cycle needs to be repeated in 2-3 weeks to resolve the infection.
Intestinal parasite hypersensitivity

Certain intestinal parasites (ascarids, Coccidia, hookworms, tapeworms, whipworms) can cause severe pruritus in certain canines. It is thought to be a type I hypersensitivity.

**Clinical signs**

Can vary but some patients can have papules, crusts, seborrhea, and sometimes even hives related to this disease.

**Diagnosis**

Positive fecal and/or response to treatment.

**Treatment**

Proper anti-helminth based off of fecal analysis.

Flea allergies

Depending on your location flea allergies can be the most common allergic hypersensitivity dermatitis you see or not present at all.

**Clinical lesions**

Intense pruritus centered around the dorsal L-S region, tail, flanks and inguinal region. One may also see papules in the umbilical area as a primary clinical sign. This leads to alopecia, crusting, papules and pustules and acute moist dermatitis “hot spots”.

**Diagnosis**

Presence of adult fleas, flea feces or based off the majority of the clinical signs being in back half of the body.

**Treatment**

Client education about the flea life cycle. One must ensure that all animals in the house are on proper, consistent flea medications all year round in some areas. Question owner regarding feral cats and other wildlife that could contribute to the flea burden in their environment and necessitate environmental control as well. Sometimes you need to treat the patient as if it is a flea allergy and then see how patients responds to therapy.

Food allergies

It is noted that 33-50% of all dogs diagnosed with a food allergy are less than 1 year of age. There is no breed or sex predilection.

**Clinical lesions**

Some patients do not exhibit any clinical lesions beyond pruritus. Some patients have chronic otitis externa as their only clinical sign of a food allergy. Erythema, papules, macules, excoriations, ulcerations, alopecia, lichenification, and hyperpigmentation can occur on the interdigital region, axillae, groin, perineal area and face. Some patients will also have concurrent GI disease which may include: vomiting, diarrhea, increased bowel movements, flatulence, and fecal mucus.

**Diagnosis**

Perform a strict 6-12-week diet trial with a hypoallergenic diet approved for growth. This includes Royal Canine Venison and Potato, Royal Canine HP, and Purina HA.

**Treatment**

Continue to feed the hypoallergenic diet or do individual ingredient re-challenge to determine exactly what patient is allergic to.

Atopy

Typically presents between the ages of six months and three years but clinicians have seen it appear as young as three months. However, many times it will take many months to come to this diagnosis since it is one of exclusion and other allergies and parasitic diseases must be explored.

**Clinical signs**

Pruritus, erythema, papules, excoriations typically occur, in the axillary region, inguinal, interdigital, muzzle, periocular, pinnae and the medial aspects of the thoracic legs. Patients may be year round or seasonal depending on the allergens they are sensitivity.

**Diagnosis**

Exclusion of other pruritic disorders. According to Favrot in order for a patient to be considered atopic they must satisfy five of the following criteria:

1. Onset of clinical signs younger than 3 years of age
2. Must live mostly indoors
3. Steroid responsive itchiness
4. Itchiness with no skin lesions
5. Front feet are affected
6. Pinna are affected
7. Ear Margins are not affected
8. Back is not affected

**Treatment**

Antihistamines, topical therapy, fatty acids, cyclosporine, steroids, immunotherapy, monoclonal antibody.

Idiopathic pruritus of puppies

First documented by Danny Scoot from Cornell University where he described ten puppies that started with pruritus between 2-7 months of age. All puppies had no history of a change in diet or environment and all were properly dewormed.
Clinical lesions
Pruritus with no clinical lesions

Diagnosis
Difficult to diagnosis properly since really a diagnosis by exclusion

Treatment
None in the puppies documented by Scott. The pruritus just resolved between 3 ½ to 5 months after onset.

References
New Drugs in Dermatology
Allison Kirby, DVM, DACVD
Animal Dermatology Clinic
Marina Del Rey, CA

Oclacitinib (Apoquel®)
Oclacitinib is approved by the FDA for the control of pruritus associated with allergic dermatitis and control of atopic dermatitis in dogs at least 12 months of age\(^1\). Apoquel\(^{\circledR}\) is the first selective Janus kinase (JAK) inhibitor developed for the dog. JAKs play a key role in cytokine signaling and the signal transduction of pro-inflammatory, pro-allergic, and pruritogenic cytokines. Although multiple JAKs exist, Apoquel\(^{\circledR}\) preferentially inhibits JAK-1\(^1\), which is involved with the signaling pathways for IL-2, 4, 6, 13, and 31\(^1\). Apoquel has the greatest affinity for inhibition of JAKs involved with IL-31 signaling, the cytokine recently demonstrated to play a central role in the development of pruritus. Apoquel\(^{\circledR}\) is administered at 0.4-0.6mg/kg twice-daily for the initial two weeks and then decreased to 0.4-0.6mg/kg once-daily for long-term use. The medication is available in 3.6mg, 5.4mg and 16mg tablets and it is recommended to administer in full and \(\frac{1}{2}\) tablet increments. The absolute bioavailability of oclacitinib maleate was found to be 89% and has been shown to have a rapid onset of action, significantly decreasing pruritus within the first 24 hours of administration\(^2,3\).

This medication is not recommended for use in patients with previous history of neoplasia. Side effects seen with this medication over a study period of 4 months include pyoderma, non-specified dermal lumps, otitis, vomiting, diarrhea, histiocytoma, cystitis, anorexia, lethargy, yeast skin infections, pododermatitis, lipoma, polydipsia, lymphadenopathy, nausea, increased appetite, aggression, and weight loss. On average, dogs gained 4% body weight on oclacitinib maleate during one study period\(^4\). Generalized demodicosis and viral papillomatous have also been seen post-approval and during initial dosing studies. Co-administration of this medication and cyclosporine and/or corticosteroids is not recommended for long term. However, a study was recently published where oclacitinib was administered with cyclosporine for a period of three week in laboratory beagles and there were no adverse events seen.\(^5\)

However, long term studies will be needed before it is deemed safe to use these two medications concurrently.

It is off label to use the medication in cats but numerous veterinarians and specialists are experimenting with its role in both feline allergic dermatitis and feline asthma. There has been one published study where 12 suspected atopic cats were treated with a mean dose of 0.47mg/kg twice daily for 14 days and then once daily for another 14 days to judge clinical efficacy. Five of these cases seemed to achieve good improvement in resolution of clinical lesions and decrease in pruritus. The remained seven either dropped out of the study due to poor response or there was no change in clinical lesions or pruritus.\(^6\)

Canine atopic dermatitis immunotherapeutic®
The USDA conditionally licensed product CADI is a caninized anti-IL-31 monoclonal antibody developed by Zoetis. Monoclonal antibody therapy works by one of two mechanisms; either by binding a soluble molecule and preventing it from interacting with a cell surface receptor or by targeting the cell surface receptor directly. CADI works by “soaking up” circulating IL-31 produced by lymphocytes preventing it from activating cell receptors. It is administered as a subcutaneous injection given no more frequently than every 30 days. CADI therapy offers the several advantages in that it is a very targeted therapy whose adverse event profile appears to be very narrow at this time. It can be administered to any age of dog, and may be given with any concurrent medications. Studies at this time reveal administration of CADI significantly reduced pruritus upon IL-31 challenge for up to a month compared to a placebo\(^7\). These studies also demonstrated that the efficacy was dose dependent with few anti-drug antibodies (ADA) produced. Finally, the efficacy and safety of CADI in field conditions compared to a placebo was evaluated and revealed that treated dogs had a significant reduction in owner assessed pruritus compared to placebo treated dogs\(^8\). The clinical improvement can be seen within 1-3 days post injection and was effective in around 80% of patients\(^7\). During initial studies no dogs developed serious adverse reactions, no dogs developed immediate post-injection reactions, and the most commonly reported adverse events were vomiting, diarrhea, and lethargy\(^7\). Given this is a caninized monoclonal antibody it will not have a place in the treatment of the feline patient. During the study period many patients were also on corticosteroids, cyclosporine, antifungals, antibiotics, immunotherapy, and/or oclacitinib and there were no complications found with administration of these medications together. Laboratory beagles have received 7 monthly subcutaneous injections at 3.3mg/kg and 10mg/kg and no side effects have been reported in this population.

CADI is available in 10mg, 20mg, 30mg, and 40mg sterile single-use preservative-free 1 ml vials that need to be kept refrigerated.

MicroSilver BG™
Microsilver BG™ is a micronized form of silver that is found in a line of topical products made by Vetbiotek. For a long time, silver has been known for its ability to kill yeast and multi-drug resistant bacterial infections; but it’s main clinical advantage comes from its activity against biofilms\(^9\). Biofilm organisms have an inherent resistance to antibiotics, disinfectants and germicides. It has been shown that up to 96% of Staphylococcus pseudintermedius isolates from canines have the ability to form biofilms\(^10\). Unlike planktonic populations, bacterial cells embedded in biofilms exhibit intrinsic resistance to antibiotics due to several specific defense mechanisms conferred by the biofilm environment, including the inactivation of anti-microbial agents by exopolysaccharide (EPS),...
over expression of stress-responsive genes, oxygen gradients within the biofilm matrix and differentiation of a subpopulation of biofilm cells into resistant dormant cells. The intrinsic resistance of bacterial cells within biofilms to conventional anti-microbials has led to new technology for the treatment of biofilm-associated infections, including the use of silver preparations. Silvers inherit anti-bacterial properties and low toxicity towards cells and make it heavily used in the human field to reduce nosocomial infections.

Vetbiotek has brought this technology into a line of shampoos, sprays, mousses and wipes that contain a silver molecule that is 10 microns in diameter. This size molecule is large enough that it will stay on the surface of the stratum corneum and not penetrate into the layers of the epidermis. In addition, the microsilver BG™ molecule is porous and adheres very well to the skin and will stay in contact with the skin until mechanically washed off; this allows for sustained anti-microbial effect. The silver molecule is also present in their seborrhea and anti-itch products.

**Osurnia®**

This is an otic gel with 10 mg florfenicol, 10 mg terbinafine, and 1 mg betamethasone acetate per mL that has been manufactured for the treatment of yeast and bacterial canine otitis externa. It is prepared in a 1ml sterile flexible soft tip applicator and one tube should treat one ear. The medication must be refrigerated upon arrival to the hospital and to increase patient comfort it should be warmed up slightly before use. The medication is then instilled in a clean and dry external ear canal and then the base of the canal is massaged to allow for the product to adhere to the lining and then also travel down the ear canal. This entire administration is then repeated in one week. This medication can be used for a suspected otitis externa with mainly cocci and/or yeast found on cytology. However, if the cytology confirms the presence of mainly rods this medication has been shown to not be very effective given the antibacterial medication present. This medication, like claro™, offers many advantages to the client and veterinarian in that all administrations could theoretically occur in the clinic. The medication would be administered at the initial visit and then the one week follow up. This increases client compliance and allows for the infection to be rechecked in a timely manner. Using a gel topical product also decreases the ability of the medication to exit the ear canal by intense head and ear shaking during the application process.

After application of this product it is recommended to not clean the ear for a total of 45 days. This recommendation stems from an ear swab depletion study that was performed with this medication in normal dogs. Normal dogs were administered the medication on day 0 and then repeated at day 7 and then drug concentrations of florfenicol, terbinafine, and betamethasone were gathered over the period of 45 days. It was concluded that after 45 days therapeutic concentrations of osurnia remained present in normal ears. However, it is suspected that concentrations of these medications in inflamed ears may be decreased due to increased absorption through the disrupted skin barrier and drug degradation secondary to inflammation.

This medication has not been tested in patients with a perforated tympanic membrane, or in animals that are pregnant or lactating. Safety studies have shown that when the 1ml product is re-administered once weekly for a total of five weeks there has been mucosal necrosis and ulceration seen of the lining of the middle ear cavity. At the recommended dosage administration patients have experienced elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), vomiting and hearing loss.

**Claro™**

This is an otic solution that contains 15.0 mg/mL florfenicol, 13.3 mg/mL terbinafine and 2.0 mg/mL mometasone furoate. It is prepared in a 1ml sterile tip applicator and one tube should treat one ear no matter what the size of the patients ear canal. Just like Osurnia™, this medication is mainly used for the treatment of otitis resulting from Malassezia pachydermatis and Staphylococcus pseudintermedius. If rods are seen on cytology and Pseudomonas spp. are suspect this medication should not be used.

This medication should be applied once in the veterinary hospital and does not need to be refrigerated. This medication has been found to remain active in the ear canal for 30 days so re-administration is not necessary.

This medication has not been tested in patients with a perforated tympanic membrane, or in animals that are pregnant or lactating. Safety studies have shown that when five times the recommended amount of medication is applied every two weeks for three applications patients can experience a dose dependent suppression of the adrenal cortical response to ACTH stimulation and have clear ear exudate and ear wetness. At the recommended dosing administration, no elevations were seen in the liver enzymes but thickening of the tympanic membrane was noted in one patient.

**Sublingual immunotherapy (SLIT)**

Allergen specific immunotherapy in veterinary and human patients for many years relied on the administration of subcutaneous injections. However, recently in both fields there has been evidence that allergens administered directly into the oral cavity can be well tolerated and effective for the treatment of spontaneous atopic dermatitis. In the veterinary field the clinical studies are limited to one in particular out of the University of Wisconsin where 10 dust mite sensitive dogs with Atopica dermatitis underwent a 6-month trial of SLIT. During the initial phase of this study, corticosteroids were needed to provide temporary comfort for patients while the immunotherapy was being introduced. However, after 4-6 months into the immunotherapy 4/10 patients stopped steroids all together and maintained comfortable and another 4/10 had a reduced steroid intake.
In another clinical trial, 49% of 47 dogs that had failed injection immunotherapy responded to SLIT that was started with the same ingredients after they failed the injection route. This is consistent with experimental evidence that shows that the mechanism of SLIT is somewhat different than that of injection immunotherapy. Side effects seen with SLIT include facial pruritus, vomiting/diarrhea, and increase in clinical signs.

Prescription Diet® Derm Defense™ made by Hills

The goal of nutrition management for canine atopic dermatitis is to inhibit inflammatory response, stabilize the skin barrier and support skin and coat health. Hills has recently released this diet to aid in the treatment of the atopic patient and is meant to be used once adverse reactions to food has already been ruled out. This diet has been fortified with what hills is calling the HistaGuard Complex™ which is a proprietary blend of whole egg, antioxidants, Vitamin E and polyphenols. These ingredients are meant to stabilize inflammatory cells and to decrease their histamine and cytokine release. Components within eggs have been shown to have an immunomodulation and anti-oxidant effect. Hills et al performed an internal study where dogs were divided into three groups; one ate a diet without egg, another group also ate a diet without egg and was given an immunosuppressive doses of steroid, and the last group ate a diet with egg. This study was for a period of 12 weeks and the group that ate the diet enriched with eggs and the steroid receiving groups each had significant decreases in their wheal diameter and thickness.

Polyphenols, which can be found in the histaguard complex™ have been found to play an inhibiting role in the presentation of allergens to the immune system, an inhibitory role in T cell release of cytokines, inhibition on B cell production of IgE and inhibition of degranulation of mast cells. In addition, these polyphenols have anti-oxidant activity limiting the free radical cell injury that can occur.

This diet is also fortified with Vitamin E which has been shown to be clinically effective for the treatment of atopic dermatitis. One study reported low serum Vitamin E concentrations in canines with atopic dermatitis. When these patients were supplemented with 8.1IU/lb of Vitamin E they developed lower CADESI scores over time.

Omega Fatty acids levels also play a critically important role with this diet. Omega 3 and 6 fatty acids are important in skin healing and its resistance to producing inflammatory cytokines. When choosing a diet or a supplement one would want low total Omega6 to omega 3 ratio because this is considered more anti-inflammatory. While total omega 6 intake can be important for minimizing transepidermal water loss and repairing epidermal defects. In terms of actual fatty acid amount, it has been discussed that 180mg/ 10lbs is the ideal amount of EPA levels for allergic patients and per feeding recommendations Derm Defense™ has 252mg/10lbs.

This diet has undergone several clinical studies, with the main one being an 8 week feeding study of atopic patients. During this study all patients were allowed to be on concurrent allergy medications (except oclacitinib) and the diet was part of the multimodal approach to therapy. At the end of the 8 weeks 65% of veterinarians and owners felt the diet made enough of a difference to warrant continued use.

References
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The Pemphigus complex is a group of autoimmune skin diseases that can affect dogs, cats, horses, people and rarely goats. By far the most common disease of this group is pemphigus foliaceus (PF), with pemphigus vulgaris (PV), pemphigus erythematosus (PE), paraneoplastic pemphigus (PNP) and pemphigus vegetans (PVeg) being considered rare. PF was first seen in the canine species in 1977 by Halliwell and Goldschmidt and the first reported case of Feline PF was in 1982. PF in animals is a pustular and crusting disease rather than a vesicular disease as seen in humans.

Incidence/prevalence
When looking at the Incidence of this disease it is difficult since there are only a few studies and there may be differences based on regions. It is suspected that PF accounts for up to 1/3 of all autoimmune diseases seen in the canine. Canine breeds that genetically predisposed include: Akitas, Chow Chow, Bearded collie, Newfoundland, Schipperke, English bulldogs and Dobermans.

Pathogenesis
PF is associated with acantholysis which occurs when there is a loss of adhesion between keratinocytes. This loss of adhesion results from disruption of desmosome junctions. Cadherins are the structures that bridge the gap between two adjacent keratinocyte cell membranes and are very important adhesion proteins. They consist of desmogleins (Dsg1–3) and desmocollins (Dsc1–3). These are the targets in pemphigus with the major antigen in canine PF appearing to be Dsc1.

Clinical lesions
The main clinical feature are pustules (vary in color) that develop in waves and evolve rapidly into crusts and sometimes erosions. They are present on the face, dorsal muzzle, peri-ocular skin, pinnae and planum nasale. Foot pads can also have extensive hyperkeratosis/crusting and fissuring. Pruritus can be present in 25-50% of cases and generalized erythema can also be seen. Some patients can also present with more systemic signs including anorexia, fever, depression and weight loss.

Diagnosis
Diagnosis requires biopsy. Since dermatophytosis can sometimes mimic clinical signs and histopathology (especially in cats) sometimes special stains are needed. In-house cytological examination of pustule contents will demonstrate acantholytic keratinocytes either individually or in rafts. There may also be extensive amount of non-degenerative neutrophils.

Treatment
The first step in the treatment of any autoimmune disease will be to perform baseline serum chemistry, complete blood count and a urinalysis in order to have a reference once treatments are started. In addition, once must ensure that any recently used medications that could have been implicated as a cause of a drug induced pemphigus reaction are stopped.

Antimicrobials
Many times at initial presentation these patients are actively infected with either bacterial or yeast infections. Ideally I like to base my antibiotic choice based off culture given these patients are going to be immunocompromised for quite some time and so medications may need to be extended. Many times patients will appear to not respond to initial coarse of immunosuppressive medications and it is because their secondary infections have not been properly addressed.

Glucocorticoids
The main stay and the first drug of choice when dealing with pemphigus patients. One of the few times steroids should not be considered as first line therapy is if a patient is concurrently diabetic. which does occur on occasion and represents a clinical challenge. Generally, once the diagnosis is established that patient is started at immunosuppressive doses of a glucocorticoid in order to get that patient into remission. The choice of glucocorticoid depends on the patient and the clinician. If that patient already has a tendency to develop PU/PD on steroids or has concurrent heart disease, I will tend to gravitate towards the medications that have less or no mineralocorticoid activity. Also many times it is not uncommon for a patient to have a better clinical response with one steroid over another.

Dose
Prednisolone/Methylprednisolone/Prednisone are used between 2.2-6 mg/kg/day but this author rarely goes over 3mg/kg/day. The immunosuppressive doses of triamcinolone is considered to be 0.2-0.6mg/kg/day and dexamethasone at 0.2-0.4mg/kg/day. When used as sole therapy it is ideal to get to 1mg/kg/EOD for prednisolone/methylprednisolone; triamcinolone to 0.1-0.2 every 2-3 days.
and dexamethasone at 0.05-0.1mg/kg every 2-3 days at maintenance. It is not uncommon for feline patients to require significantly higher dose of oral steroids to achieve remission, immunosuppressive dosages range from 2.2 to 8.8 mg/kg/day for prednisolone. Two studies have shown that 33-38% of canine patients can respond with the use of glucocorticoids alone. I personally feel that felines many times will respond to steroids alone and this percentage may be higher is this species (around 65% or higher). 7

Monitoring
In the ideal situation the immunosuppressive doses are continued for 10-14 days and then gradually tapered to maintenance level over a period of 6-12 weeks. This requires recheck examinations every 2 weeks for the first 2-3 months in the best case scenario. At each recheck I recommend serum chemistry/complete blood counts to be performed and a urinalysis and culture done at 2-3 months into therapy. The urine culture is to ensure that a patient has not developed a urinary tract infection that can commonly occur with long term steroid use. The serum chemistry and CBC is to ensure there are no signs of hyperglycemia or severe hepatic dysfunction. At each recheck cytology is performed to evaluate the presence or absence of acantholytic cells and bacteria/yeast. If a large number of acantholytic cells are found generally I will continue the immunosuppressive doses for 2 more weeks and then recheck the patient two weeks later.

If unable to taper the dose of steroids due to lack of improvement of clinical signs or worsening of clinical disease upon taper one must either add in additional immunosuppressive medications or change the formulation of steroids.

Adverse events
Complications with steroids are vast given their general mechanism of action. Given the haptic changes that occur with glucocorticoids and many of the other immunosuppressive drugs it may be beneficial to also start hepatic support medications (SAM-E) at the time of diagnosis. Many patients will also suffer PU/PD/PP/panting, muscle atrophy, poor dull scaly hair coats, wt gain, behavior changes, increased risk for infections (bladder infections, demodicosis, dermatophytosis), comedones, atrophic skin, calcinosis cutis, atrophic scars, milia GI ulcerations, diarrhea and and decreased thyroid hormone, adrenal gland suppression, Diabetes mellitus.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Glucocorticoid activity</th>
<th>Mineralocorticoid activity</th>
<th>½ life (hours)</th>
<th>Equivalent dose mg</th>
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<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>8-12</td>
<td>20mg</td>
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<td>Prednisolone/</td>
<td>4</td>
<td>0.8</td>
<td>12-36</td>
<td>5</td>
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<td>prednisone</td>
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<td></td>
<td></td>
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<tr>
<td>Methylprednisolone</td>
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<td>0.5</td>
<td>12-36</td>
<td>4</td>
</tr>
<tr>
<td>Triamcinolone</td>
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<td>0</td>
<td>24-48</td>
<td>0.5-1</td>
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<tr>
<td>Dexamethasone</td>
<td>25-30</td>
<td>0</td>
<td>36-72</td>
<td>.75</td>
</tr>
</tbody>
</table>

Azathioprine (Imuran®)
Azathioprine (AZA) is considered an antimetabolite agent whose main mechanism of action involves mimicking natural molecules utilized in DNA and/or RNA replication. As a group they are most active in the 'S' phase of the cell cycle (when DNA is being synthesized). Immuran serves as fraudulent purine bases during DNA and RNA synthesis, resulting in dysfunctional nucleic acid strands in proliferating cells. The T-lymphocytes, T-cell dependent antibody synthesis, and cell mediated immunity) are inhibited, with very little direct effect on B-cells. AZA is metabolized into 6-mercaptopurine (6-MP) by the liver and then 6 MP is metabolized by three different enzymes. Two of these enzymes are xanthine oxidase and TPMT (thiopurine methyltransferase) which produce inactive compounds. In general, patients with low TPMT activity, have a greater incidence of bone marrow suppression, but also greater immuran efficacy. As a species cats have low activity of TPMT, hence this medication is not recommended for these patients. Dogs have variable amounts of TMPT activity levels similar to that seen in humans, which may explain why some canine patients respond better and/or develop more myelotoxicity than others. Giant Schnauzers are known to have very low TMPT whereas Alaskan Malamutes have very high TMPT activity.

Dose
When used in combination with oral steroids the dose varies from 1 to 2.5mg/kg Q24 to 48 hours) or 50 mg/m2. Supplied as 50mg tablets and there is a very slow onset of action. Typically, beneficial response in seen within 6-12 weeks

Monitoring
CBC/chem after 2 to 3 weeks, then again in 1 month, then quarterly. Some clinicians monitor more frequently (Q2 weeks for the first 8 week). Watch the lymphocytes and platelet counts for decreasing trends, which may indicate when to decrease the dose.
**Adverse events**

Include bone marrow suppression and hepatopathy (contraindicated in cats). There has been an association with pancreatitis when used concurrently with prednisolone. Diarrhea is the most common side effect along with opportunistic infections. There has been rare hepatotoxicity that does respond to drug withdrawal.

**Chlorambucil**

This medication is considered to be an alkylating agent that affects disease by physiochemical interaction with pre-formed and developing DNA and RNA. These medications as a group exert their effect (cross-links, strand breaks) on all stages of the cell cycle (i.e., do not require an actively proliferating population). As a group they are cytotoxic to all lymphocyte populations (including B-cells) and very effectively suppress immunoglobulin secretion. The new formulation requires refrigeration. It is considered to be the drug of choice for cats. It can also be used in conjunction with steroids.

**Dose**

0.1-0.2 mg/kg q 24-48 hrs ONLY 2 mg tablets

**Monitoring**

CBC at 2 weeks and CBC chem. 4 weeks, then CBC at 8 weeks; Delayed action 2-4 weeks.

**Adverse events**

Myelosuppression, anorexia, vomiting, diarrhea

**Cyclosporine**

Cyclosporine is considered a calcineurin inhibitor that leads to the blocking of IL-2 transcription which results in impaired T helper and T cytotoxic lymphocytes (remember the principal action of IL-2 is T cell proliferation). Reduces production of IL-2, IL-3, IL-4, G-CSF and TNF-alpha as well as reducing the clonal proliferation of the cell. This leads to decreased clonal proliferation of B lymphocytes and indirectly also effects other cells, such as granulocytes, macrophages, NK cells, eosinophils and mast cells. Although initial studies have shown that food affects absorption when clinical efficacy studies were done with atopic patients no change was seen.

**Dose**

5-10mg/kg Po SID

**Monitoring**

CBC/chem/UA after first 1-2 months and then every 6 months there after

**Adverse Events**

GI disturbances (vomiting, diarrhea, decreased appetite), gingival hyperplasia, papillomatous growths, increased susceptibility to opportunistic infections, hypertrichosis

**Tacrolimus**

The topical calcineurin inhibitor preparation is used mostly in veterinary medicine for localized lesions of PF and PE. It is the first macrolide immunosuppressant discover. It was found in a soil fungus, although it is produced by a type of bacteria, *Streptomyces tsukubaensis*.

**Dose**

Generally used twice daily

**Adverse events**

Minimal

**Tetracycline/doxycycline and Niacinamide**

The mechanism of action of this pair of medications is not exactly known. Tetracycline/doxycycline have been known to have anti-inflammatory properties affecting complement activation, antibody production, chemotaxis, prostaglandin synthesis, and suppressing lymphocyte blastogenesis. Niacinamide blocks antigen and immunoglobulin E induced histamine release, inhibits mast cell degranulation and phosphodiesterase protease release. This pair does have a delayed onset of action and generally beneficial response is seen after 6-12 weeks.

**Dose**

Doxycycline 5mg-10 mg/kg Po BID and Niacinamide is dosed at 250mg PO TID less then 10kgs; 500mg MG/KG greater then 10kg

**Monitoring**

Serum chem and CBC every 6 months

**Adverse events**

Vomiting, diarrhea are the most common Doxycycline can also cause esophageal stricture in cats and dogs
Mycophenolate Mofetil
Derived from the fungus Penicillium stoloniferum and is metabolized in the liver to mycophenolic acid (MP). This compound is a potent and reversible uncompetitive inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH). This inhibition leads to the synthesis of guanine being blocked and prevents DNA and RNA synthesis. Cytotoxic to cells that rely on de novo purine synthesis (such as T and B lymphocytes)\(^{11}\).

**Dose**
22-39 mg/kg daily divided into q8 hour dosing; available in 250 and 500 mg. tablets

**Monitoring**
No clear protocol set, Complete blood count and serum chemistry q2-4 weeks for the first 2-3 months then every 6 months

**Adverse events**
Myelosuppression, Gastrointestinal upset: vomiting, diarrhea, anorexia and Increased risk of infections (urinary tract, skin, etc.) The concurrent use of mycophenolate and azathioprine is not recommend based off their similar mode of action\(^{12}\).

Leflunomide
Is a pyrimidine synthesis inhibitor that works by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase. This enzyme is involved in the de novo synthesis of the pyrimidine ribonucleotide uridine monophosphate (rUMP). Also Antagonizes action of IL-3, IL-4 and TNF-α

**Dose**
2-4 mg/kg per day\(^{13}\)

**Monitoring**
No set protocol, CBC serum chem UA after 2 weeks and then every 3 weeks for 3 months. In one paper leflunomide dosage was decreased by 25% every 4 weeks for the first 4 months in order to achieve a trough level of approximately 20 micrograms/mL (leflunomide trough levels were based on studies of the canine renal transplantation model); then the dosage was decreased every 8 weeks until discontinuation after 10 months of therapy\(^{14}\).

**Adverse events**
Hepatotoxicity, myelosuppression (leukopenia, anemia and thrombocytopenia), recurrent infections, pneumonia and cutaneous drug eruptions

Human IVIG
Sterile purified IgG that is pooled from human plasma, that may also contain traces of IgA and IgM\(^{15}\). The exact mechanism of action is not known so there are several theories on how this medication works. Blocks the Fc receptors on antibiotics and eliminates circulating immune complexes, suppressing anti-idiotypic autoantibodies, inhibits complement mediation damage, and blocks the cell surface death receptor Fas have all been discussed\(^{16,17}\).

**Dose**
0.5-2.2 g/kg given slowly IV over 6-12 hours\(^{14,18}\).

**Monitoring**
Has a similar set up and monitoring as a blood transfusion to ensure no signs of anaphylaxis.

**Adverse events**
Allergic reaction, In human’s hypertension, nausea, tachycardia can occur. There has only been limited studies on the re-administration of IVIG to canine patients and this should be done with caution.

References
Managing Chronic Otitis: The Keys to Getting Started on the Right Foot

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The 2013 and 2014 data from Veterinary Pet Insurance lists ear infections as the number TWO reason that dogs went to veterinarians (after “skin allergies”) for veterinary care. In addition, Banfield data indicates that otitis was the second most common diagnosis made in affiliated hospitals in 2011. This data has been similar every year since 2005, with otitis being the #1 or #2 most common presenting complaint in dogs, year after year.

There are many, many important concepts about otitis that can literally make the difference in practice. Knowledge can, in fact, change your entire attitude about dealing with ear disease.

Information needed to manage otitis (getting started on the right foot)

#1 – Understanding structure and function
The ear consists of the pinna, the external ear canal, the middle ear, and the inner ear. There are major variations in the anatomy from breed to breed, especially with respect to the length and diameter of the external ear canal. These variations will affect predilection for disease, diagnosis, and treatment. For example, it can be very difficult to fully examine the external canal of the ear of an Irish setter, for it can be very long!

The external ear canal consists of skin overlying the auricular and annular cartilages. It has a vertical component and a horizontal component. The vertical component is formed by the auricular cartilage. The annular cartilage is the rolled, tube-like cartilage that extends from the auricular cartilage at the base of the vertical ear canal to the temporal bone. The auricular cartilage overlaps the annular cartilage with a fibrous band, which allows for flexibility in movement.

Anatomically, the vertical canal is more open and larger in volume than the horizontal ear canal. There is a depression or pocket at point where the auricular and annular cartilages overlap (i.e., the “opening” of the horizontal canal). The entrance to the horizontal canal is often elevated and requires manipulation of the otoscope in order to pass it into the horizontal canal. There is actually a fold of skin (overlying cartilage) on the dorsal aspect of the canal that must be bypassed in order to slip the otoscope into the horizontal ear canal. Mechanical irritation (e.g., during otoscopic examination) of this fold will cause startle the patient and result in poor patient compliance with otoscopy.

The skin lining the ear canal has sebaceous glands and apocrine (i.e., ceruminous) glands throughout the length. Sebaceous glands are found in the superficial part of the dermis with the apocrine glands located deeper. These apocrine glands can open directly onto the surface of the skin or in the hair follicle. Hair follicles are found throughout the length of the ear canal in most breeds, but there is breed variation as to the type of follicles and their density.

Ear wax is the mixture of apocrine (cerumen) gland secretions, sebaceous secretions, and epithelial cells. There is a natural movement of sebum outwardly in the normal ear, facilitating natural cleaning and removal of sebum.

The lipid portion of ear wax is derived from sebaceous glands and contains various waxes and fatty acids, many of which are bacteriostatic and fungistatic. The lipid portion of cerumen is responsible for controlling microorganisms. The apocrine secretions (from “ceruminous glands”) produce a water-based secretion that contains phospholipids and IgA, which also contributes to the defense of the ear. Epithelial cells contribute to the texture and consistency of the wax. Increased epithelial cell production in the ear will produce a thicker, pasty ear wax.

The tympanic membrane is at the end of the external ear canal. On otoscopic examination, the tympanum appears as a vertically aligned structure, but it actually is sloped at approximately a 30° angle, with the top towards the viewer. The tympanic membrane consists of two parts. The pars tensa is the tightly stretched, clear to opaque whitish section of the tympanic membrane. Embedded within the pars tensa is the handle (aka manubrium) of the malleus, the largest ossicle of the middle ear. The malleus is curved, with the concave section pointing rostrally. The pars flaccida is the dorsal-rostral component of the tympanic membrane. It appears pink and there are often small capillaries visible on the surface of the membrane. The pars flaccida often bulges out and may be seen moving with respiration, in a movement that resembles the bulging throat of a bullfrog!

The tympanum in the cat is much more transparent, and thus is often thought to be absent. The malleus is straighter than in the dog and the pars flaccida is generally not visible. Cats also have a bony septum in their middle ear that runs rostral to causal….and this septum tends to obstruct the view of the middle ear during otoscopic examination and creates an obstruction for materials inside the middle ear. The two-chambered nature of the middle ear in the cat impairs our ability to clean and perform various procedures in the middle ear in cats.
2. Understanding the pathophysiology of otitis

By now, everyone should know about the concepts on the pathophysiology of otitis as introduced by Dr. John August. He recommended dividing the pathogenic factors of otitis as follows:

1. Predisposing factors: these are conditions that "set the ear up" for inflammation. They include conformational changes, behavior, and previous treatments.
2. Primary factors: these are those conditions that initiate inflammation in the ear. They include allergic diseases, foreign bodies, ectoparasites, autoimmune and other inflammatory skin disorders, and trauma.
3. Perpetuating factors: these factors keep the inflammatory process active and often make it significantly worse. Perpetuating factors include bacterial infections, yeast infections, hyperplastic changes, and otitis media.

Simply put, there is a “WHAT” and a “WHY” when dealing with ear disease. Clinicians must address both or the problem will fail to resolve or recur.

3. Understanding pathologic changes in the ear

Once the otitis has begun, certain pathologic changes occur that initiate a cascade of events that make the ear more hospitable for microorganisms and reduce the lumen size of the ear canal. Inflammatory changes are accompanied by pain, and progressive disease leads to loss of hearing. It has been determined that the pathologic changes in the ear do reduce acuity of hearing, and that some of that hearing loss is reversible, as the pathologic changes are reversed.

With inflammation comes edema and infiltration of inflammatory cells. Secretion of various growth factors will result in epidermal hyperplasia and hyperkeratosis, resulting in microfissures on the surface of the skin and increased deposition of cornified keratinocytes in the lumen of the ear. As inflammation progresses, there is fibroplasia (i.e., fibrosis) of the dermis and subcutis. Chronic inflammation of the cartilage will result in ossification of these structures.

Within the dermis, it has been shown that apocrine glands increase in size in otitis externa. The intense inflammation around apocrine glands, combined with epidermal hyperplasia (papillary proliferation) results in occlusion of ductal openings on the skin and hair follicles and may predispose the gland to rupture. When the apocrine glands rupture, there is infiltration of lymphocytes, neutrophils, mast cells, and macrophages into surrounding tissue. It would appear that the disruption of these glands significantly contributes to the inflammation, pain, and fibrosis. Interestingly, sebaceous glands remain the same size, even in chronic otitis externa, though there is a qualitative change in sebum production. The net result is decreased lipid content of cerumen in ears with otitis externa. Since lipid secretions of the skin have barrier and antimicrobial functions, there is speculation that this change contributes to secondary infections in otitis externa.

Finally, biopsy of the ear canal in chronic otitis externa will reveal folliculitis and furunculosis. With furunculosis there is release of keratinized materials into the dermis, and the net result is a foreign body-type reaction. Furunculosis is common in ceruminous otitis externa associated with familial seborrhea of the American cocker spaniel.

4. Knowing the goal: Restoring defense mechanisms of the ear

The ear does have an effective defense system. First there is an inherent self-cleansing mechanism. Debris, including desquamated keratinocytes and wax, naturally moves from deep into the canal to the opening of the canal. Anything that blocks this movement, such as a foreign body or scar tissue, will predispose to infections. Second, ear wax is an amazing antimicrobial material, along with its other functions. Third, the hair in the canal and at the opening of the canal does help to restrict access into the canal. Again, this has both good and bad aspects.

Diagnostic approach to otitis

Collection of a thorough dermatologic history is crucial to evaluate the patient for the primary factor (i.e., underlying cause, or the "why"). When it comes to managing the perpetuating factors (e.g., current infections), it is helpful to know what medications have been used in the past. This includes amounts, frequency, and duration of each treatment. The physical examination includes inspection and palpation of the entire ear canal. The mouth should be opened wide to evaluate for bullae pain, one possible indicator of otitis media.

Otoscopy should be performed on all cases, and repeated at each recheck of the patient. Both ears should be examined, even if the client believes the problem is unilateral (one ear is often worse than the other). Handheld otoscopes are very useful and there are different styles that have different levels of magnification. Several commercial video otoscopes are now affordable and they provide much better visualization down the canal.

Cytology is the key diagnostic procedure in otology. Cytology should be done on both ears and repeated at every recheck examination...because things to change in the canal. Samples are usually collected by passing a cotton-tipped applicator gently into the ear canal to the beginning of the horizontal canal. If resistance is encountered while passing the swab, it should not be advanced further! The swab is gently rotated then withdrawn and used to make “roll preps” on a clean glass microscope slide. The slide is then stained (with the stain of choice in your practice) and examined under the microscope.

A couple of tips for cytology:
1. Use a clean glass slide (wipe the slide with a gauze to make it clean)
2. Use firm pressure to roll the swab (this will increase the adhesion of material)
3. Dip or place slides into jars of stain or fixative VERY gently. Do not move the slide up and down after the initial placement…you may gently sway the slide in the jar to distribute stain, if needed.
4. Rinse the slide immediately after the thiazine (blue) stain (when using Diff-Quik stain), BUT do not let the rinse water hit the sample directly.
5. Air dry or use a blow dryer with the heat coil turned off to rapidly dry the slide. Do not overheat (or the sample may be ruined)!

Tips:
1. Make two ear prep slides on each case and examine before cleaning the ears, in the event that a culture is indicated.
2. Stain one slide with Diff-Quik and save the other for a Gram stain, to be done if rod-shaped organisms are present on the initial slide.

A normal ear may contain low numbers of bacteria (usually cocci) and yeast. However, the absolute number (e.g., number of organisms per field of view) is not important, since we all make slides differently. The cytologic findings are correlated with the clinical findings and a decision made to treat is based on all data.

Bacterial culture is indicated when: 1) the cytology shows a uniform population of rod-shaped bacteria (probably *Pseudomonas* spp.), 2) the infection has failed to respond to “standard-of-care” therapy, 3) when you have a known resistant organism (generally based on previous culture results). Imaging of the ear can also be very helpful. Radiography may help identify bony changes in the bullae that might reflect otitis media. Computerized tomography provides much better detail and is the author’s imaging of choice, due to relative low cost and high degree of detail provided. Magnetic resonance imaging is also very helpful, however the cost is significantly higher than CT scanning.

**Client education and communication**

Client education starts on day 1….the first time you see a client/pet with otitis. Client education should include:

1. Some basic information about the pathophysiology of otitis (really important),
2. Information about your plan for their pet (i.e., identify secondary issues, treat those, then look for the underlying cause),
3. Diagnostic findings on their pet at the first visit,
4. Why the recheck exam is important and what will happen at that appointment (repeating diagnostics, switching from treatment to a maintenance plan, additions testing for primary factors, etc.),
5. The long-term picture of otitis

   It is very helpful to use analogies when speaking to clients. The author uses the analogy of archeology: dermatology and otology problems are like archeology. That is, clinicians must keep on digging until they find the underlying civilization (i.e, primary factor). If the clinician does not address the underlying problem, then the perpetuating (i.e., secondary) factors will fail to respond to treatment or will recur. So, it makes sense to explain this to clients at the beginning, understanding that it is unlikely that a client will give consent to spend a lot of time and money searching for a cause of first-time otitis. But….you plant the seed by giving them the education about the pathogenesis of otitis. That way, when the problem recurs (notice I didn’t say “if”), they just may remember that you tried to explain this to them.

   Ear models are great for explaining otitis. Several companies have provided these to veterinarians in the past, so ask your reps about one! It is especially helpful to explain the “L” shaped ear canal and why we have to medicate the way we do.

   Last, video otoscopes also help the clients be more involved. Clients LOVE seeing their pet’s ears before and after cleaning or before and after treatment. Letting clients see the ears will definitely help to convince them that cleaning and medications are warranted.

   The clinical effects of client education include: better client compliance, more cooperative clients, and better success. Everybody wins.
Managing Chronic Otitis:  
Tips to Maximize the Value of Your Treatment  
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Topical therapy is the most commonly used treatment for otitis externa. Selection of active ingredients and treatment protocols for veterinary otic preparations tend to have been driven by the pharmaceutical industry based on guidelines to facilitate approval by various governmental and regulatory agencies. The term best practices implies a method or technique set forth by an authority that has consistently shown superior results to those achieved with other means, and that are used as a benchmark. Ideally, these serve as clinical treatment guidelines and are integral to evidence-based practice of medicine.

Important concepts prior to treatment

1. A reminder of the structure and function (anatomy and physiology) of the ear is crucial. Specifically, the shape of the ear canal provides some challenges for topical therapy.
2. A reminder of the pathophysiology of otitis is also important: we have predisposing factors, primary causes (or underlying factors), and perpetuating factors (secondary causes) in otitis. There is a difference between short-term management (and success) and long-term management (and success).
3. Client education is paramount. It is essential that clients understand the two points listed above AND the goals and expectations of treatment.
4. We need to have collected the right information to allow us (the veterinarian) to “choose wisely” the best topical medication for each possible combinations of problems that may be factors in each patient. We need to know “what” is going on in the ears.

Cleaning the ears: “Preparing to succeed”

Cleaning the ears is an important and crucial component of effective management of chronic ear disease in dogs and cats. Cleaning the ears is important for the following reasons:

1. Cleaning removes debris, such as wax, that may cause irritation of the ear canal.
2. Cleaning removes debris that will block movement of medication into the horizontal canal and the self-cleansing mechanism.
3. Cleaning removes debris (e.g., pus, biofilm) that can interfere with the activity of topical (and systemic) otic medications.
4. Cleaning may help to lower the burden of bacteria in the ear.

The cleaner you get the canal, the better the chances are that your topical medication will work. Keep in mind that the efficacy of some topical medications, such as polymyxin B sulfates and some aminoglycosides, is dramatically reduced in the presence of pus! So, it is to your patient’s and client’s advantage to start with an ear cleaning.

It is your choice, as the veterinarian, on which type of ear cleaning you select. For mild cases, it may suffice to use a basic technique of filling the canal with cleanser, massaging the canal, then removing excess cleanser and debris with a cotton ball...repeated until otoscopic exam confirms that most of the debris has, in fact, been removed. However, I recommend a deep ear cleaning (or ear flush) with the patient under general anesthesia if you are unable to definitively see the ear drum...or at least enough to confirm that it is intact.

A good rule of thumb: Deep ear cleaning or flushing (under general anesthesia) is indicated if you cannot definitively visualize the tympanic membrane prior to treatment.

Best practices for topical management of otitis externa

Overall, the long-term success of medical management of otitis externa depends on the following considerations:

- Obstructions, such as hair and wax, should be removed to allow distribution of medications deep into the ear canal
- Topical medications should be selected based on consideration of the active ingredients and data supporting the use of that agent for secondary infections or perpetuating factors
- The integrity of the tympanic membrane should be considered when selecting topical medications
- The formulation of the medication should allow the product to distribute deep into the canal and provide adequate coverage of the surface area of the ear canal
- Topical medications must be administered using proper technique to ensure delivery of medicine throughout the full extent of the external canal. This often includes “positional instillation” of medicine, which means positioning the animal (on its side, for example) to allow deeper movement of the agent into the ear canal.
- Adequate volumes of topical medications must be administered to reach the deeper aspects (proximal) of the ear canal
Treatment of infections should be continued until the infection is cleared. Generally, this requires a treatment period of 3-4 weeks.

Ear medications are most often in the form of an ointment (emulsions of lipid in water) or as a solution (aeroseous or other carriers). Emulsions containing lipids will enhance penetration of the active ingredient into the skin of the ear; however, most of these ointment formulations are so viscous, that they fail to penetrate down deep into the ear canal. They are especially ineffective in the presence of a heavy growth of hair in the canal. Less viscous medications are more likely to allow medication to distribute deeper into the canal, especially when there is significant hair in the ear canal or when the canal is hyperplastic. There is little data on the overall effect of viscosity on “spreadability” or distribution of topical medications over the skin that lines the ear canal.

In all cases when topical therapy is used, the owners MUST be educated about application of medications. This should include having the owner instill medication, IN THE PRESENCE of the veterinarian or technician. Owners should be taught to massage ears for 15-30 seconds after instilling medications, and to use proper amounts of medications. Once-daily treatment is generally sufficient for most cases of otitis, though severe infections may benefit from twice daily treatment. Treatment should be continued until there is no clinical or cytologic evidence of active disease. The minimum recommended treatment time (with topical therapy) is 30 days.

**Dose (volume) recommendations**

- Small dogs (<15 kg): 0.4-0.5 ml
- Medium dogs (15-20 kg): 0.7-0.8 ml
- Large dogs (>20 kg): 1.0 ml

The volume of medication applied into the ear during treatment appears to be critical. Dosing syringes work well to accurately measure volumes of otic medications. Failure to apply sufficient quantities to penetrate to these areas seems to be a major cause of treatment failure. Volumes recommended in this paper to achieve adequate penetration down the canal are based on existing literature and pilot studies performed by the author. You may increase movement of otic medicine deeper into the canal by using “positional installation” and by massaging the ear for 15-30 seconds after instillation.

Keep in mind that higher volumes of otic medication may increase the likelihood of absorption of otic medications, especially glucocorticoids. It is important to understand that there may be systemic side effects as more potent glucocorticoids are used.

**Table 1. Commercial veterinary otic preparations**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Drops/ml*</th>
<th>Label dosing</th>
<th>Maximum tx time (days)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurizon®**</td>
<td>Vétoquinol</td>
<td>?</td>
<td>10 drops once daily</td>
<td>7-14</td>
</tr>
<tr>
<td>Baytril® Otic</td>
<td>Bayer Animal Health</td>
<td>30</td>
<td>&lt;35 lbs: 5-10 drops twice daily; &gt;35 lbs: 10-15 drops twice daily</td>
<td>14</td>
</tr>
<tr>
<td>easOtic®</td>
<td>Virbac Animal Health</td>
<td>NA</td>
<td>1 pump daily</td>
<td>5</td>
</tr>
<tr>
<td>Mometamax®</td>
<td>Intervet/Schering Plough Animal Health†</td>
<td>40</td>
<td>&lt;30 lbs: 4 drops once daily; &gt;30 lbs: 8 drops once daily</td>
<td>7</td>
</tr>
<tr>
<td>Otomax®</td>
<td>Intervet/Schering Plough Animal Health†</td>
<td>37</td>
<td>&lt;30 lbs: 4 drops twice daily; &gt;30 lbs: 8 drops twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Posatex™</td>
<td>Intervet/Schering Plough Animal Health†</td>
<td>39</td>
<td>&lt;30 lbs: 4 drops twice daily; &gt;30 lbs: 8 drops twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Surolan®</td>
<td>Vetoquinol</td>
<td>45</td>
<td>5 drops twice daily</td>
<td>7</td>
</tr>
<tr>
<td>Tresaderm®</td>
<td>Merial</td>
<td>40</td>
<td>5-15 drops twice daily</td>
<td>7</td>
</tr>
</tbody>
</table>

* Determined manually by author. Estimates ± 2 drops/ml. ** Not available in USA
† Merck Animal Health USA ‡ Label instructions
Table 2. Newer extended-activity otic preparations

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Active ingredients</th>
<th>Labeled dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>KetoCort®</td>
<td>TrilogicPharma</td>
<td>Ketoconazole, hydrocortisone</td>
<td>Clean ears and dry. Instill adequate amount and repeat as necessary.</td>
</tr>
<tr>
<td>Osurnia®</td>
<td>Elanco</td>
<td>Florfenicol, terbenifine, betamethasone</td>
<td>Clean ears and dry. Instill one tube, massage 1-2 minutes Repeat in one week.</td>
</tr>
<tr>
<td>Claro™</td>
<td>Bayer</td>
<td>Florfenicol, terbenifine, mometasone</td>
<td>Clean ears and dry. Instill one tube.</td>
</tr>
</tbody>
</table>

The integrity of the tympanic membrane is critical in determining the best treatment options for a patient with otitis. The possibility of ototoxicosis is greatly enhanced if the medication is instilled directly into the middle ear. The best practice is to avoid topical therapy, if the tympanic membrane is torn or absent. However, there are some clinical indications, based entirely on anecdotal evidence, that vinegar: water (1:2) and enrofloxacin (parenteral formulation) are fairly safe.

Topical therapy is considered sufficient to manage most cases of otitis externa, if the principles of therapy discussed early are followed. In general systemic therapy is indicated when:

- The infections are recurrent and severe
- There are concurrent infections elsewhere, such as the skin, that would respond to the therapy
- When the owners are incapable of treating topically (e.g., arthritis, elderly owner)
- When the patient is entirely uncooperative
- When there is severe hyperplastic changes in the canal that preclude the ability of topical medications to distribute deeper into the ear canal

Systemic antibacterial therapy is indicated when inflammatory cells are seen on cytology, when a pure infection of a gram-negative bacteria is present, in recurring bacterial infections, when ulcers are present in the external ear canal, or when systemic signs accompany the otitis. Systemic therapy may or may not be indicated when otitis media is present. The antibiotic selection depends upon the organism isolated. Drugs should be dosed at the high end of the recommended range….always go up on pill size, never skimp on systemic drug doses! Drugs should be administered for a minimum of three weeks, then the patient re-examined and evaluated with cytology and/or culture.

Lastly, you should consider the goal of your therapy. Practically speaking, it is the improvement of the clinical condition of otitis: reduced swelling, erythema, pain, and restoration of function. However, for longer-term success in managing ear disease, it is important to CLEAR the infections. This generally requires longer treatment periods and higher doses.

Future considerations

There are several areas where additional studies could be greatly beneficial. For example, there is little data on contact times required, in vitro and in vivo, for effective killing/clearance of various bacteria and yeast. In addition, it would be helpful to better understand the distribution of topical medications, both immediately after instillation and after 12 and 24 hours following administration. We have little data about the duration of inhibitory concentrations of antimicrobials over time after topical application.

Selected references and recommended readings

Managing Chronic Otitis: Treating the Difficult Case and Preventing Recurrence

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Iowa State University
Ames, IA

Most difficult problems in otology can be resolved if best practices are followed. However, there are several conditions which seem to be considered more difficult and frustrating, depending on the situation. They include:

1. management of allergic ears
2. management of recurring yeast infections
3. control of specific bacterial infections, such as Pseudomonas infections
4. management of ceruminous otitis (seborrheic ear disease)
5. control of severe hyperplastic changes
6. treatment of otitis media

In this session, we’ll address Pseudomonas infections and hyperplastic changes and talk about strategies to prevent recurrence.

Pseudomonas infections
Pseudomonas aeruginosa is a hydrophilic, beta-lactamase producing, gram negative bacterium that is commonly associated with otitis externa and media in the dog. Many strains of Pseudomonas (up to 40% of isolates) are known to be potent producers of biofilm, a matrix that coats the surface of the tissue and “protects” the organisms from antimicrobial activity. Biofilm-producing bacteria had significantly higher MICs for common pathogens isolated in canine otitis. Biofilm is known to physically block penetration of compounds, such as antibiotics and antiseptics, and create concentration gradients of these agents that reduce efficacy and may lead to antimicrobial resistance. Remove or reduction of biofilm is a key component of managing patients with Pseudomonas infections.

Proper cleansing of the ear, systemic therapy with an appropriate antimicrobial agent, and management of the primary factor are also part of managing Pseudomonas infections of the ear! Aggressive and thorough cleaning of the ear is crucial to remove the biofilm, and thus allow the treatment of choice to be effective. There are limited studies reported at this time demonstrating the effectiveness of various cleansers or otic medications in the presence of biofilm.

Antibiotic therapy of Pseudomonas otitis
Antibiotic treatment of recurring Pseudomonas infections (or other resistant gram negative infections) should be based on cytology and culture results. Appropriate antibiotic stewardship is strongly encouraged when making the clinical decision to use an antibiotic. Some topical treatment options include:

- Gentamicin (Otomax/Mometamax/Posatex-ScheringPlough-Merial) is an effective antimicrobial for many Pseudomonas infections. Unfortunately, the labeling on this product in the USA minimizes its effectiveness (dose volume, maximum treatment period).
- Topical tobramycin (available as generic ophthalmic drops)
- Polymyxin B (Surolan®-Vetoquinol). Many Pseudomonas isolates are sensitive to this antibiotic; however, polymyxin B sulfates are not active in the presence of supplicative inflammation. Synergy of polymyxin B and miconazole against E. coli and Pseudomonas isolates (but not Proteus isolates) from dogs with otitis externa has been demonstrated in vitro.
- Topical fluoroquinolone antibiotics (Baytril® Otic-Bayer, Aurizon®-Vetoquinol) are often effective for Pseudomonas infections.
- Other antibiotics from which topical otic medications may be formulated include amikacin, (1-2%), ceftazidime, imipenem and meropenem. The latter two drugs have restricted use in most hospitals (for life-threatening infections) to prevent resistance. Their use should be as a last resort and therapy should follow all principles of antimicrobial use to avoid contributing to bacterial resistance to these drugs.

Additional topical therapy includes agents that may not have direct antibacterial activity, but that are used to support other antimicrobial products.

- Tromethamine (Tris) edetate disodium dehydrate (EDTA), known more commonly as Tris-EDTA solution, is commonly used as adjunctive therapy for bacterial otitis. Several commercial products (e.g., TrizEDTA™ Aqueous Flush-Dechra, and T8 Keto® Flush-DVM) contain this solution. There is good evidence that the Triz-EDTA is highly effective for Pseudomonas when used concurrently with an appropriate antimicrobial (some fluoroquinolones or aminoglycosides), silver sulfadiazine, or chlorhexidine. Triz-EDTA alone is bacteriostatic in vitro, but is not bactericidal. Triz-EDTA has been shown in vitro to reduce the MICs for neomycin and gentamicin (but not enrofloxacin or polymyxin B) for biofilm-embedded bacteria. Additional studies show that Triz-EDTA enhances antibiotic efficacy of marbofloxacine and gentamicin against multidrug-resistant Pseudomonas in vitro. Clinically, these products are often
administered into the infected ear 15-30 minutes prior to an antibiotic; however, data suggests they may be administered concurrently. Tris-EDTA appears to be safe when instilled into the middle ear, but there is no evidence to support that clinical observation.

Antiseptic therapy for *Pseudomonas* *otitis*

Antiseptics are attractive alternatives to the use of antibiotics for control of bacterial skin and ear diseases. However, most studies involving their use for *otitis* are in vitro studies looking at MIC values. It is likely that the ultimate effectiveness of antiseptics will involve selection of the proper concentrations (to exceed MICs or minimum bactericidal concentrations) and also consider the contact time.

- Silver sulfadiazine (SSD), (Baytril® Otic-Bayer) or as a 19 dilution of the 1% silver sulfadiazine cream. SSD has been shown to be effective in vitro against *Pseudomonas*. Based on two studies, it appears that the MICs for *Pseudomonas* have increased in the past 30 years (from 7.5 ug/ml to 23.4 ug/ml); however, they are still low enough to easily treat ears topically with available products. Note: The addition of Tris-EDTA to SSD has been shown to decrease the MIC even lower.
- Acetylcysteine has been shown to have anti-*Pseudomonas* activity in vitro, with the MIC values for six isolates calculated to be 10.3 mg/ml. Clinical trials (in vivo studies) have not been reported.
- Aluminum acetate; Burow’s solution has been demonstrated to have activity against *Pseudomonas* in vitro and in some animal models of *Pseudomonas*-associated otitis media. Clinical studies are ongoing in dogs with *Pseudomonas* otitis. Interestingly, aluminum acetate is a component of many commercial products in the USA that are used for managing otitis.
- Chlorhexidine and other antiseptics/biocides have efficacy against *Pseudomonas* and have been combined in various ear cleansers with Tris-EDTA for enhanced activity. There have been conflicting reports of the ototoxicity of chlorhexidine.

One very important key to successful treatment of *Pseudomonas* otitis, is the concurrent use of glucocorticoids, preferably systemically. Glucocorticoids reduce the pain that is associated with this condition- and thus will make application of topical medications easier and more effective. In addition, glucocorticoids reduce the inflammation, which also reduces the discomfort and swelling that accompanies this condition. The recommended dose of prednisone in dogs is: 1-2 mg/kg. PO once daily for 5-7 days, then every other day for 5 doses, then half of the dose every other day for 5 additional doses. Naturally, any allergy testing should be done prior to initiation of glucocorticoid therapy.

Patients with *Pseudomonas* infections tend to get other secondary infections, most often yeast infections, immediately after the *Pseudomonas* is cleared. Therefore, we often initiate prophylactic anti-yeast therapy as part of our maintenance therapy as soon as the bacterial component of the otitis is controlled.

Lastly, control of the underlying cause (or primary factor) is very important to prevent recurrence, and in some cases, may be necessary to get the problem under control.

**Hyperplastic changes**

Swollen ear canals are a major threat to the survival of the ear! Hyperplastic changes of the external ear canal include epidermal hyperplasia (e.g., lichenification), fibrosis, edema, glandular hyperplasia, and inflammation, especially folliculitis and furunculosis. Hyperplastic changes are perpetuating factors. They promote a microclimate favoring microbial growth (increased temperature and humidity) and physically prevent distribution of topical medications deep in the ear. In addition, they reduce the ability of veterinarians to adequately examine or clean the ear. Closure of the ear canal may be due to 1) edema and inflammation or 2) fibrous changes, including calcification of the canal. It is difficult clinically determine whether the hyperplastic changes are reversible (due to edema and inflammation) or permanent (fibrosis). To make that determination, the following is recommended:

1. Potent topical glucocorticoids are administered to reduce inflammation. The glucocorticoid is should be in a vehicle that allows and facilitates deep movement into the canal (e.g., Synotic®-Ft. Dodge containing DMSO and flucinolone). An adequate volume should be instilled 1-2 times daily to reach the deeper areas of the ear canal. If flucinolone is not available, mometasone (Claro-Bayer) may be infused into the ear if the canal is patent enough to allow infusion.
2. Since distribution of a topical drug may not reach deep into the canal, concurrent administrations of a systemic glucocorticoid is recommended to reduce edema and allow for a proper examination or to allow medication to gain access to the ear. Assuming there are no medical conditions that may preclude their use, prednisone or prednisolone may be administered orally (1-2 mg/kg daily for 5-7 days, then q 48 hour for 5 doses, then half the dose every other day for 5 additional doses).

Patients are re-examined in 3-4 weeks. If the ear canal has opened (indicating the changes were primarily edema and inflammation), efforts should be directed towards identifying and managing the primary and perpetuating factors. If the canal does
not significantly open with topical and systemic administration of glucocorticoids, triamcinolone may be injected (0.05 mL/site) in a spiral manner in the most severe areas, in an attempt to reduce edema and inflammation. Alternatively, long-term administration of cyclosporine may benefit some of these ears. It is unclear whether any effect of cyclosporine is due to anti-inflammatory actions or control of underlying primary factors of otitis. However, if the canal has become calcified, a total ear canal ablation is recommended.

Preventing recurrence

An important strategy for all ear infections is to aggressively treat and clear the infection using best practices as described previously. However, the next step in management of otitis is to recheck and re-evaluate the patient to determine if the infection has been reduced/suppressed, or cleared. There is a big difference.

A recheck examination should be performed in each patient at an interval when the veterinarian feels the infection should be cleared. At that time, the examination should include 1) history since treatment was initiated, 2) physical examination, 3) cytology examination, 4) cytology of the ear, and in cases with recurring infection or gram negative bacterial infections, 5) repeated culture. If cytology and culture (when performed) are negative, we proceed to the next step.

Maintenance therapy is always begun on patients with chronic otitis as soon as the recheck examination suggests the infection is cleared. The goals of maintenance therapy include 1) keeping the ears clean, 2) control or decreasing pain and pruritus, 3) control or decreasing the number of infectious agents, and 40 promoting “normalization” of the ear. The principles include the intermittent use of cleansers and non-antibiotic therapeutics (e.g., antiseptics, non-antibiotic agents) to prevent recurrence of the infection OR to reduce the severity and frequency of secondary infections. Options maintenance therapy include use of cleansers proven to have antimicrobial activities (e.g. EpiOtic Advanced-Virbac; Malacetic Otic-Dechra). Ingredients with antiseptic properties include salicylic acid, boric acid, parachlorometaxylenol, and chlorhexidine. Other ear products and “flushes” that contain benzoyl alcohol (T8Keto-Bayer), aluminum acetate (Burow’s solution, CortAstrin-VedCo) also have antibacterial and/or antifungal activity. Some otic products (MalAcetic Ultra-Dechra) contain azoles for managing yeast infections. We do not fully comprehend the ability of Malassezia pachydermatis to develop resistance to intermittent exposure to these agents, so caution should be the rule when looking for long-term maintenance of yeast infections.

Ultimate control

In the final analysis, identification and control of the underlying primary factor of the otitis will lead to the best long-term management. However, some clients are unwilling or unable to pursue those factors due to financial consideration, medical philosophy, distrust of the motives of the veterinarian, or a lack of will. Maintenance therapy is ALWAYS combined with client education to achieve the best results for each patient.

Summary

Most difficult cases of otitis externa are not due to resistant organisms or strange circumstances. Most difficult cases develop when there has been a breakdown in communication or failure to strictly adhere to the best practices of ear management. Proper and thorough cleaning of the ears is a necessity in the management of chronic otitis externa. Infectious components of otitis can be managed and controlled, though in some cases, repeated trials may be required to identify the best treatment. Long-term control of otitis externa or media requires identification and management of the primary factors.

Selected references and recommended readings


